Mailbox
09/512701

-Key terms

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FILE 'REGISTRY' ENTERED AT 11:59:29 ON 06 MAR 2001
             E INTERLEUKIN 12/CN 5
L1            43 S INTERLEUKIN 12 ?/CN
             E "INTERLEUKIN-12"/CN 5
L2             1 S E4
L3            43 S L1 OR L2

FILE 'CAPLUS' ENTERED AT 11:59:58 ON 06 MAR 2001
L1            43 SEA FILE=REGISTRY ABB=ON  PLU=ON  INTERLEUKIN 12 ?/CN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "INTERLEUKIN-12 (HUMAN
                 CLONE PEF-BOS P40 SUBUNIT)"/CN
L3            43 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 OR L2
L4          5201 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 OR IL12 OR (INTERLEUKI
                 N OR IL)(W)12 OR (NATURAL KILLER OR NKC)(1W)STIMULAT?
                 FACTOR
L5           132 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 AND (RA OR RHEUMAT?
                 ARTHRIT?)
L6            79 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 AND (TREAT? OR
                 THERAP?)
L7            23 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 AND ADMIN?

L7  ANSWER 1 OF 23  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:911120  CAPLUS
DOCUMENT NUMBER:          134:55498
TITLE:                    Compositions and methods for the
                          treatment or prevention of autoimmune
                          disorders using DNA vaccine encoding a
                          self-antigen
INVENTOR(S):              Von Herrath, Matthias G.
PATENT ASSIGNEE(S):       The Scripps Research Institute, USA
SOURCE:                   PCT Int. Appl., 55 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE          APPLICATION NO.  DATE
     ----------------    ----  --------      ---------------  --------
     WO 2000078360       A1    20001228      WO 2000-US16218  20000613
         W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
            CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
            ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
            LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
            RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ,
            VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
            CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
            BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                              Searcher  :  Shears  308-4994
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PRIORITY APPLN. INFO.: US 1999-336672 19990617

AB The present invention provides compns. and methods for the prevention or **treatment** of autoimmune disorders using DNA vaccine encoding a self-antigen. In particular, the invention methods utilize plasmid vector encoding at least a portion of an autoreactive epitope that, upon **administration** to a subject, acts to modulate the immune system thereby ameliorating conditions assocd. with an autoreactive antigen. The compns. and methods of the invention include co-**administration** of another vector encoding a biol. response modifier (e.g., a cytokine, chemokine, interferon, interleukin) for the effective induction of regulatory cytokines to down-regulate the immune system of a mammal having an autoimmune condition. The invention is exemplified by the **treatment** or prevention of insulin dependent diabetes in a murine model using RIP-LCMV-NP: transgenic mouse line that expresses lymphocytic chiromeningitis virus nucleoprotein under control of the rat insulin promoter. The exemplary autoreactive epitope used is from insulin .beta. chain. RIP-NP transgenic mice are **treated** with pCMV-NP with pCMV-ins-B and LCMV-specific CTL responses are evaluated. The studies compare the progression of diabetes in immunized and non-immunized mice and show that the transfer of splenocytes from insulin-B protected mice prevents IDDM and the self-reactive (LCMV-NP) CTL activity in pCMV-B protected mice is reduced.

REFERENCE COUNT: 3

REFERENCE(S):

(1) Nicolette, C; WO 0020457 A 2000 CAPLUS
(2) Univ Southern California; WO 9745144 A 1997 CAPLUS
(3) Von Herrath, M; JOURNAL OF IMMUNOLOGY 1998, V161(9), P5087 CAPLUS

L7 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:535166 CAPLUS

DOCUMENT NUMBER: 133:129859

TITLE: Inhibition of STAT3 signal transduction and the **treatment** of cancer in humans

INVENTOR(S): Jove, Richard; Dalton, William; Sebti, Said; Yu, Hua; Heller, Richard; Jaroszeski, Mark

PATENT ASSIGNEE(S): University of South Florida, USA

SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044774	A2	20000803	WO 2000-US1845	20000127

Searcher : Shears 308-4994

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-117600 19990127

AB Signal Transducer and Activator of Transcription (STAT) proteins have a fundamental role cell signaling, and are activated by a large no. of cytokines and growth factors. One member of the STAT family, STAT3, has a crit. role in oncogenesis. The present invention relates generally to disruption of the pathway of STAT3 signaling in the **treatment** of human cancer. STAT3 activation is shown to be present in diverse tumor cell lines and tumors, to promote oncogenesis, to inhibit apoptosis, and to reduce sensitivity to chemotherapeutic agents. Inhibition of STAT3 signaling induces apoptosis specifically in tumor cell lines, and increases sensitivity to chemotherapeutic agents. The invention relates more particularly to methods, compns., means of **administering** such compns., and means for identifying such compns. for the inhibition of STAT3 intracellular signaling in the **treatment** of human cancers. Activation of STAT3, as measured EMSA, was inhibted in tumor cell lines by inhibitors of Src and Jak protein tyrosine kinases. The Jak kinase inhibitor AG490 blocked the proliferation of human mammary tumors in nude mice. Blocking of serine phosphorylation of STAT3 had similar effects.

L7 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:405017 CAPLUS

DOCUMENT NUMBER: 133:133995

TITLE: Retinoid-mediated inhibition of **interleukin-12** production in mouse macrophages suppresses Th1 cytokine profile in CD4+ T cells

AUTHOR(S): Kang, B. Y.; Chung, S. W.; Kim, S. H.; Kang, S. N.; Choe, Y. K.; Kim, T. S.

CORPORATE SOURCE: College of Pharmacy, Chonnam National University, Kwangju, 500-757, S. Korea

SOURCE: Br. J. Pharmacol. (2000), 130(3), 581-586
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1 **Interleukin-12** (**IL-12**) plays a central role in the immune system by driving the immune response towards T helper 1 (Th1) type responses characterized by

high IFN-.gamma. and low IL-4 prodn. In this study the authors investigated whether retinoid-mediated inhibition of **interleukin-12** prodn. in mouse macrophages could regulate cytokine profile of antigen (Ag)-primed CD4+ Th cells. 2 Pretreatment with retinoids (9-cis-**RA**, all-trans-**RA**, TTNPB) significantly inhibited **IL-12** prodn. by mouse macrophages stimulated with lipopolysaccharide (LPS) or heated-killed Listeria monocytogenes (HKL). Retinoid-pretreated macrophages reduced their ability to induce IFN-.gamma. and increased the ability to induce IL-4 in Ag-primed CD4- T cells. 3 Addn. of recombinant **IL-12** to cultures of retinoid-pretreated macrophages and CD4+ T cells restored IFN-.gamma. prodn. in CD4+ T cells. 4 The in vivo **administration** of 9-cis-**RA** resulted in the inhibition of **IL-12** prodn. by macrophages stimulated in vitro with either LPS or HKL, leading to the inhibition of Th1 cytokine profile (decreased IFN-.gamma. and increased IL-4 prodn.) in CD4+ T cells. 5 These findings may explain some known effects of retinoids including the inhibition of encephalitogenicity, and point to a possible **therapeutic** use of retinoids in the Th1-mediated immune diseases such as autoimmune diseases.

REFERENCE COUNT: 27

REFERENCE(S):
(1) Caspi, R; Clin Immunol Immunopathol 1998, V88, P4 CAPLUS
(3) Constant, S; Annu Rev Immunol 1997, V15, P297 CAPLUS
(4) Dekruyff, R; J Immunol 1995, V154, P2578 CAPLUS
(5) Dekruyff, R; J Immunol 1998, V160, P2231 CAPLUS
(6) D'Elios, M; Transplant Proc 1998, V30, P2373 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:175933 CAPLUS
DOCUMENT NUMBER: 132:218023
TITLE: Prostate-specific promoter for the regulation of gene expression and gene **therapy** of prostate diseases
INVENTOR(S): An, Gang; Veltri, Robert
PATENT ASSIGNEE(S): Urocor, Inc., USA
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014234	A1	20000316	WO 1999-US20544	19990907
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9958156	A1	20000327	AU 1999-58156	19990907
PRIORITY APPLN. INFO.:			US 1998-99338	19980908
			WO 1999-US20544	19990907

AB Disclosed are compns. and methods of use of the promoter for prostate-specific transglutaminase. Prostate-specific transglutaminase, as well as cytokeratin 15 and semenogelin II are differentially expressed in prostate disorders. Prostate-specific expression and dramatic down-regulation in high Gleason grade and metastatic prostate cancer make the prostate-specific transglutaminase gene specifically useful in the **treatment** of prostate disease. The invention relates particularly to isolated nucleic acids and vectors comprising the sequence of this promoter. The invention also relates to methods of **therapeutic treatment** for prostate cancer or benign prostatic hyperplasia (BPH) utilizing this promoter. Described are means for the isolation and identification of transcriptional factors and other DNA-binding proteins that regulate promoter transcriptional activity, identification of regulatory elements within the promoter and construction of deletion mutants contg. specific subsets of these regulatory elements, identification of small mol. ligands that bind to and inhibit or activate the identified transcriptional factors and other DNA-binding proteins, construction of vectors contg. the prostate-specific transglutaminase promoter operatively linked to genes of use in the **treatment** of prostate cancer or BPH, and methods for **treatment** of prostate cancer or BPH by **administration** of such vectors to patients with prostate cancer or BPH. Further described are methods for **treatment** of prostate cancer or BPH by **administration** of small mol. ligands that bind to and inhibit or activate transcriptional factors or other DNA-binding proteins that regulate the activity of this promoter.

REFERENCE COUNT: 1
REFERENCE(S): (1) Dubbink Hendrikus, J; European Urology, Meeting Info: 13th Congress of the European Society for Urological Oncology and Endocrinology 1998, V34(3), P255

Searcher : Shears 308-4994

L7 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:122524 CAPLUS
DOCUMENT NUMBER: 132:161002
TITLE: Divergent effect of cyclosporine on Th1/Th2 type cytokines in patients with severe, refractory **rheumatoid arthritis**
AUTHOR(S): Kim, Wan-Uk; Cho, Mi-La; Kim, Sung-Il; Yoo, Wan-Hee; Lee, Shin-Seok; Joo, Young-Shil; Min, Jun-Ki; Hong, Yeon-Sik; Lee, Sang-Heon; Park, Sung-Hwan; Cho, Chul-Soo; Kim, Ho-Youn
CORPORATE SOURCE: Center for Rheumatic Diseases, Research Center in Catholic Medical Center, Department of Internal Medicine, Kang-Nam St. Mary's Hospital, Catholic University of Korea, Seoul, S. Korea
SOURCE: J. Rheumatol. (2000), 27(2), 324-331
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: To investigate the effect of cyclosporine on cytokine prodn., esp. on T helper 1 (Th1) and T helper 2 (Th2) type cytokines, in patients with **rheumatoid arthritis** (**RA**). A 16 wk randomized, double blind, placebo controlled study of cyclosporine (2.5 to 4 mg/kg/day) was conducted in 40 patients with severe, refractory **RA** who had residual inflammation and disability despite partial responses to prior maximal tolerated dose of methotrexate (MTX; < 15 mg/wk) and low dose prednisone (< 10 mg/day). Clin. and lab. variables, and circulating levels of interleukin 2 (IL-2), IL-4, IL-10, **IL -12**, tumor necrosis factor-.alpha. (TNF-.alpha.), and interferon-.gamma. (IFN-.gamma.) measured by ELISA were compared between patients (cyclosporine group) **treated** with cyclosporine plus MTX and those (placebo group) **treated** with placebo plus MTX at entry and at 16 wk. At 16 wk, the cyclosporine group (n = 17), compared with the placebo group (n = 17), had greater decreases in tender joints, swollen joints, patient global assessment, patient self-assessed disability, and C-reactive protein, as well as having more patients with > 20% improvement. Comparison of circulating cytokines at entry and at 16 wk showed significant decreases of IL-2 (median -61 vs. 7 pg/mL; p = 0.004), **IL-12** (median -313 vs. -14 pg/mL; p = 0.002), TNF-.alpha. (median -55 vs. 5 pg/mL; p < 0.001), and IFN-.gamma. (median -21 vs. 5 pg/mL; p = 0.003), and a significant increase of IL-10 (median 55 vs. -12 pg/mL; p < 0.001) in the cyclosporine group compared with the placebo group. The degree of IL-10 increases correlated strongly with the degree of **IL-12** decreases in the cyclosporine group (r = 0.572, p = 0.016). However, there was no change in circulating IL-4 between the 2

groups. Within the cyclosporine group, the improved patients (n = 10) compared to the non-improved patients (n = 7) had a greater increase in circulating IL-10 (median 172.0 vs. 85.2%; p = 0.01). The rate of increase of IL-10 strongly correlated with the rate of improvement of joint scores (r = 0.718, p = 0.001) after **administration** of cyclosporine. Our results suggest that the **therapeutic** effect of cyclosporine is achieved by correcting a Th1/Th2 imbalance (a shift of Th1 type to Th2 type), which may be involved in the pathogenesis of **RA**; and that circulating IL-10 is useful to assess the clin. improvements in patients with **RA** after **administration** of cyclosporine.

REFERENCE COUNT: 47

REFERENCE(S):
(1) Abrams, J; Immunol Rev 1992, V127, P5 CAPLUS
(3) Andersson, J; Immunol 1992, V75, P136 CAPLUS
(6) Aste-Amezaga, M; J Immunol 1998, V160, P5936 CAPLUS
(7) Bonnotte, B; Tissue Antigens 1996, V48, P265 CAPLUS
(9) Briscoe, D; J Immunol 1997, V159, P3247 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:722927 CAPLUS
DOCUMENT NUMBER: 131:335816
TITLE: Reversal of proinflammatory response by ligating the macrophage Fc.gamma.RI receptor
INVENTOR(S): Mosser, David M.; Sutterwala, Fayyaz S.
PATENT ASSIGNEE(S): Temple University - of the Commonwealth System of Higher Education, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9956777	A1	19991111	WO 1999-US9269	19990429

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9938710 A1 19991123 AU 1999-38710 19990429
PRIORITY APPLN. INFO.: US 1998-84385 19980506
WO 1999-US9269 19990429

AB Ligation of the Fc.gamma. receptor type I (Fc.gamma.RI) on IL-10-producing cells leads to a selective upregulation of IL-10 prodn., which in turn induces a marked suppression of **IL-12** biosynthesis by **IL-12**-producing cells, particularly macrophages. The ligation of the Fc.gamma.RI receptor thus down-modulates **IL-12** prodn. via a mechanism that is dependent on macrophage-derived IL-10. Agents for ligating Fc.gamma.RI comprise, for example, multivalent antibodies which bind the Fc.gamma.RI receptor, immune complexes comprising antibodies which contain the Fc region of IgG, and IgG multimers, preferably IgG dimers and trimers. The ligating agent may be **administered** to **therapeutically** inhibit proinflammatory immune responses. In particular, the ligating agent may be **administered** to **treat** or prevent endotoxic shock assocd. with bacterial endotoxemia, and to **treating** autoimmune disorders.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Deo; Immunology Today 1997, V18, P127 CAPLUS
(2) Sutterwala; Journal of Experimental Medicine 1997, V185(11), P1977 CAPLUS
(3) Sutterwala; Journal of Experimental Medicine 1998, V188(1), P217 CAPLUS

L7 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:475528 CAPLUS
DOCUMENT NUMBER: 132:21885
TITLE: Hormonal regulation of tumor necrosis factor-.alpha., **interleukin-12** and interleukin-10 production by activated macrophages. A disease-modifying mechanism in **rheumatoid arthritis** and systemic lupus erythematosus?
AUTHOR(S): Wilder, Ronald L.; Elenkov, Ilia J.
CORPORATE SOURCE: Inflammatory Joint Diseases Section, Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Ann. N. Y. Acad. Sci. (1999), 876(Neuroendocrine Immune Basis of the Rheumatic Diseases), 14-31
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 152 refs. **Rheumatoid arthritis** (

RA) and systemic lupus erythematosus (SLE) frequently develop and progress in settings in which sympathoadrenomedullary and gonadal hormone levels are changing, e.g., during pregnancy, postpartum period, menopause, estrogen **administration**. This paper addresses the view that adrenal and gonadal hormonal deficiency facilitates excessive macrophage prodn. of TNF-.alpha. and **IL-12** that characterizes **RA**, whereas excessive estrogen action is suggested to play an essential role in the prodn. of IL-10 in patients with SLE. Disease activity in SLE, in contrast to **RA**, appears to be assocd. with high-level prodn. of IL-10, relative to the proinflammatory cytokines, TNF-.alpha. and **IL-12**. Accumulating data suggest that novel **therapeutic** approaches may ultimately be developed from continued investigation of the role of the neuroendocrine factors in **RA** and SLE.

REFERENCE COUNT: 152

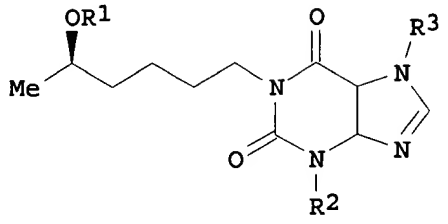
REFERENCE(S):
(1) Amico, J; Clin Endocrinol 1986, V25(2), P97 CAPLUS
(6) Bellido, T; J Clin Invest 1995, V95(6), P2886 CAPLUS
(7) Bohler, H; Brain Res Mol Brain Res 1990, V8(3), P259 CAPLUS
(10) Buyon, J; Ann Med Interne 1996, V147(4), P259 CAPLUS
(11) Buyon, J; J Leukocyte Biol 1998, V63(3), P281 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:468563 CAPLUS
DOCUMENT NUMBER: 131:102135
TITLE: Method of inhibiting **interleukin-12** signaling using 1-(5-hydroxyhexyl)-3,7-dimethylxanthine derivatives
INVENTOR(S): Klaus, Stephen J.; Klein, Peter J.; Kumar, Anil M.
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936073	A1	19990722	WO 1998-US27848	19981230

W: AU, CA, CN, CZ, HU, IL, JP, MX, NO, NZ, PL, PT, RU, YU
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,

NL, PT, SE
AU 9920987 A1 19990802 AU 1999-20987 19981230
PRIORITY APPLN. INFO.: US 1998-8020 19980116
WO 1998-US27848 19981230
OTHER SOURCE(S): MARPAT 131:102135
GI



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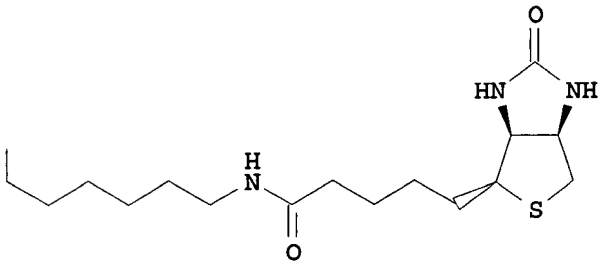

AB Described is a method for blocking **IL-12** signaling by **administration** of formula (I; wherein R1 is H, Me, sulfate, phosphate, or salt thereof; R2 is C1-12 alkyl, C1-11 alkoxyalkyl, dialkoxyalkyl, CH2Ph, -CH2-furan, biotin; R3 = H, Me or CH2Ph) in a mammal having a CD4+ Th1 cell-mediated inflammatory response. The CD4+ Th1 cell-mediated inflammatory response is selected from chronic inflammatory disease, chronic intestinal inflammation, arthritis, psoriasis, asthma, and autoimmune disorders which in turn are selected from the group consisting of type-1 insulin dependent diabetes mellitus ("IDDM"), multiple sclerosis, **rheumatoid arthritis**, inflammatory bowel disease, lupus disorders, and acute graft-vs.-host disease. Thus, (R)-3-(6-aminohexyl)-1-(5-hydroxyhexyl)-7-methylxanthine hydrochloride was condensed with biotin N-hydroxysuccinimide ester in the presence of imidazole in DMSO for 6 h to give the title compd. (I; R1 = H, R2 = Q, R3 = Me). The title compd. (I; R1 = H, R2 = R3 = Me) in vitro inhibited induction of active and passive exptl. autoimmune encephalomyelitis in mice and reduced in vivo Th1 Differentiation of MBP-specific T cells in mice, and in vitro suppressed Th1 differentiation by blocking **IL-12** signaling.

REFERENCE COUNT: 2

REFERENCE(S): (1) Bianco; US 5648357 A 1997 CAPLUS
(2) Hinze; US 4515795 A 1985 CAPLUS

L7 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:113796 CAPLUS
DOCUMENT NUMBER: 130:195740
TITLE: Membrane-bound cytokine compositions and methods of modulating an immune response using same
INVENTOR(S): Soo, Hoo William
PATENT ASSIGNEE(S): The Immune Response Corporation, USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906544	A1	19990211	WO 1998-US15622	19980728
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5891432	A	19990406	US 1997-902516	19970729
EP 1009821	A1	20000621	EP 1998-937204	19980727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 9885971	A1	19990222	AU 1998-85971	19980728
PRIORITY APPLN. INFO.:			US 1997-902516	19970729
			WO 1998-US15622	19980727

AB The present invention provides a cellular vaccine having a membrane-bound fusion protein that includes a non-antibody immunomodulatory mol. operatively fused to a heterologous membrane attachment domain. Non-antibody immunomodulatory mols. useful in the invention include immunostimulatory and immunosuppressive mols. such as cytokines. In one embodiment, the invention provides a cellular vaccine having a membrane-bound fusion protein that includes a non-antibody immunomodulatory mol. operatively fused to a heterologous membrane attachment domain and, addnl., a disease-assocd. antigen or immunogenic epitope thereof. Further provided by the invention are methods of modulating an immune response against a disease-assocd. antigen by **administering** to an individual a cellular vaccine having a membrane-bound fusion protein that includes a non-antibody immunomodulatory mol. operatively fused to a heterologous membrane attachment domain.
REFERENCE COUNT: 11
REFERENCE(S): (1) Bueler, H; Molecular Medicine 1996, V2(5), P545 CAPLUS
(2) Caras; US 5109113 A 1992 CAPLUS

(3) Cohen; US 5759535 A 1998 CAPLUS
(4) Dranoff; US 5637483 A 1997 CAPLUS
(5) Fan, X; Biochem Biophys Res Commun 1996, V225, P1063 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:85910 CAPLUS
DOCUMENT NUMBER: 130:310420
TITLE: Amelioration of collagen-induced arthritis and suppression of interferon-.gamma., **interleukin-12**, and tumor necrosis factor .alpha. production by interferon-.beta. gene **therapy**
AUTHOR(S): Triantaphyllopoulos, Kostas A.; Williams, Richard O.; Tailor, Hitakshi; Chernajovsky, Yuti
CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, W6 8LH, UK
SOURCE: Arthritis Rheum. (1999), 42(1), 90-99
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors investigated the **therapeutic** effects and possible mechanisms of action of constitutive expression of interferon-.beta. (IFN.beta.) by syngeneic fibroblasts from DBA/1 mice in the collagen-induced arthritis (CIA) model. Immortalized embryonic DBA/1 fibroblasts were infected with a retrovirus expressing murine IFN.beta.. IFN.beta.-expressing fibroblasts were then implanted i.p. into mice immunized with bovine type II collagen. The effect of IFN.beta. on paw swelling, anti-collagen antibody levels, IgG1/IgG2a isotype profiles, arthritis score, histol. joint damage, and cytokine secretion from lymph node cells and from bone marrow-derived macrophages was assessed. A single injection of IFN.beta.-secreting fibroblasts was sufficient to prevent arthritis or to ameliorate existing disease. Thus, IFN.beta. reduced the clin. score and paw swelling irresp. of whether the injection was **administered** before or after disease onset in **treated** mice, compared with that in the untreated control group. Histol. findings in the IFN.beta.-**treated** mice were markedly less severe than in the control group. This effect was accompanied by a decrease in total anti-collagen IgG levels, a decrease in anti-collagen IgG2a, and an increase in IgG1. In vitro, supernatants from these engineered fibroblasts inhibited collagen-induced interferon-.gamma. secretion from lymph node cells, and reduced the levels of tumor necrosis factor .alpha. and **interleukin-12** produced by lipopolysaccharide/IFN.gamma.-**treated** bone marrow-derived macrophages. This effect was specific, since it was reversed with

anti-IFN.beta. polyclonal antibodies. These results indicate that IFN.beta., which is currently used as a **treatment** for relapsing, remitting multiple sclerosis, is a potent immunomodulatory and anti-inflammatory cytokine in CIA and should be considered for the **treatment** of **rheumatoid arthritis**.

REFERENCE COUNT: 37

REFERENCE(S):
(1) Abu-Khabar, K; J Leukoc Biol 1992, V52, P165 CAPLUS
(2) Aebischer, P; Nat Med 1996, V2, P696 CAPLUS
(3) Almazan, G; Brain Res 1992, V579, P234 CAPLUS
(5) Arnason, B; Springer Semin Immunopathol 1996, V18, P125 CAPLUS
(6) Bandara, G; Proc Natl Acad Sci U S A 1993, V90, P10764 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:640257 CAPLUS
DOCUMENT NUMBER: 129:255530
TITLE: Methods and compositions for modulating responsiveness to corticosteroids
INVENTOR(S): Sekut, Les; Carter, Adam; Chayur, Tariq; Banerjee, Subhashis; Tracey, Daniel E.
PATENT ASSIGNEE(S): Basf A.-G., Germany
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841232	A2	19980924	WO 1998-US4916	19980312
WO 9841232	A3	20001005		
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6054487	A	20000425	US 1997-820692	19970318
AU 9867604	A1	19981012	AU 1998-67604	19980312
EP 998300	A1	20000510	EP 1998-912929	19980312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT,				

IE, FI

BR 9810409	A	20000822	BR 1998-10409	19980312
NO 9904506	A	19991117	NO 1999-4506	19990917
PRIORITY APPLN. INFO.:			US 1997-820692	19970318
			US 1998-16346	19980130
			WO 1998-US4916	19980312

AB Method for modulating responsiveness to corticosteroids in a subject are provided. In the method of the invention, an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in the subject is **administered** to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when the corticosteroid is given alone. The method can be used to, for example, reverse steroid resistance of to increase steroid sensitivity, or to ameliorate the steroid rebound effect when subjects are taken off corticosteroid **treatment**. In one embodiment, the agent is an IL-18 antagonist. In another embodiment, the agent is an **interleukin-12 (IL-12)** antagonist. In yet another embodiment, the agent is an NK cell antagonist. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-**IL-12** monoclonal antibody. In yet another preferred embodiment, the agent is an anti-asialo-GM1 antibody or an NK1.1 antibody. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the **treatment** of a variety of inflammatory and immunol. diseases and disorders. Pharmaceutical compns. comprising an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred compn. comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L7 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1998:434764 CAPLUS
DOCUMENT NUMBER:	129:201783
TITLE:	The chronobiology of human cytokine production
AUTHOR(S):	Petrovsky, Nikolai; Harrison, Leonard C.
CORPORATE SOURCE:	Autoimmunity and Transplantation Division, The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville, 3050, Australia
SOURCE:	Int. Rev. Immunol. (1998), 16(5-6), 635-649 CODEN: IRIMEH; ISSN: 0883-0185
PUBLISHER:	Harwood Academic Publishers
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review with 52 refs. Cytokine prodn. in human whole blood exhibits diurnal rhythmicity. Peak prodn. of the pro-inflammatory

cytokines IFN-.gamma., TNF-.alpha., IL-1 and **IL-12** occurs during the night and early morning at a time when plasma cortisol is lowest. The existence of a causal relationship between plasma cortisol and prodn. is suggested by the finding that elevation of plasma cortisol within the physiol. range by the **administration** of cortisone acetate results in a corresponding fall in pro-inflammatory cytokine prodn. Cortisol may not be the only neuroendocrine hormone that entrains cytokine rhythms; other candidates include 17-hydroxy progesterone, melatonin and dihydroepiandrostene dione (DHEAS). The finding of diurnal cytokine rhythms may be relevant to understanding why immuno-inflammatory disorders such as **rheumatoid arthritis** or asthma exhibit night-time or early morning exacerbations and to the optimization of **treatment** for these disorders. Diurnal rhythmicity of cytokine prodn. also has implications for the timing of blood samples drawn for diagnostic T-cell assays. Finally, diurnal rhythmicity of immune function suggests that the nature of an immune response, for example in response to vaccination, may be modified by the time of day of antigen **administration** and raises the possibility that immune responses could be **therapeutically** manipulated by co-**administration** of immuno-regulatory hormones such as glucocorticoids.

L7 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:345697 CAPLUS
DOCUMENT NUMBER: 129:121512
TITLE: Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and **therapeutic** implications
AUTHOR(S): Petrovsky, Nikolai; McNair, Peter; Harrison, Leonard C.
CORPORATE SOURCE: Walter Eliza Hall Institute, Royal Melbourne Hospital, Parkville, 3050, Australia
SOURCE: Cytokine (1998), 10(4), 307-312
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Clin. features of certain immuno-inflammatory disorders such as **rheumatoid arthritis** and asthma exhibit diurnal fluctuation, which could be related to diurnal rhythmicity of pro-inflammatory cytokine prodn. To investigate the latter, the authors performed measurements of lipopolysaccharide (LPS)-stimulated whole blood, interferon .gamma. (IFN-.gamma.), tumor necrosis factor .alpha. (TNF-.alpha.), interleukin 1 (IL-1) and **IL-12** prodn. in 13 healthy volunteers over 24 h. These cytokines exhibited distinct diurnal rhythms that peaked in the early morning and were inversely related to the rhythm

of plasma cortisol. Elevation fo plasma cortisol within the physiol. range by **administration** of cortisone acetate, 25 mg at 21.00, markedly suppressed IFN-.gamma., TNF-.alpha., IL-1 and **IL-12** prodn., but not the later early morning rise of endogenous plasma cortisol. Suppression of cytokine prodn. was temporally dissocd. from changes in nos. of circulating mononuclear cells. Regulation of pro-inflammatory cytokine prodn. by plasma cortisol has potential **therapeutic** implications. In contrast to std. schedules, a small, late evening, dose of glucocorticoid to suppress the diurnal increase in pro-inflammatory cytokine prodn. could alleviate early morning inflammatory symptoms and minimize side-effects.

L7 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:251074 CAPLUS
DOCUMENT NUMBER: 128:307519
TITLE: Methods for enhancing oral tolerance and **treating** autoimmune disease using inhibitors of **interleukin-12**
INVENTOR(S): Strober, Warren; Kelsall, Brian L.; Marth, Thomas
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA; Strober, Warren; Kelsall, Brian L.; Marth, Thomas
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9816248	A1	19980423	WO 1996-US16007	19961011
W: AU, CA, JP, US				
AU 9672576	A1	19980511	AU 1996-72576	19961011
PRIORITY APPLN. INFO.:			WO 1996-US16007	19961011

AB The present invention provides a method for enhancing oral tolerance to an antigen assocd. with an autoimmune disease in a subject having the autoimmune disease comprising orally **administering** to the subject an antigen assocd. with the autoimmune disease and **administering** an inhibitor of **interleukin-12** in amts. sufficient to enhance oral tolerance. Also provided in the present invention is a method for **treating** or preventing an autoimmune disease in a subject comprising orally **administering** to the subject an antigen assocd. with the autoimmune disease and **administering** an inhibitor of **interleukin-12** in amts. sufficient to **treat** or prevent the autoimmune disease, thereby

treating or preventing the autoimmune disease. The **interleukin 12** inhibitor is an antibody or monoclonal antibody.

L7 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:180786 CAPLUS
DOCUMENT NUMBER: 128:242897
TITLE: Immune direction **therapy**
INVENTOR(S): Prendergast, Patrick T.
PATENT ASSIGNEE(S): Prendergast, Patrick T., Ire.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810792	A1	19980319	WO 1996-IB945	19960913
W: AT, AU, BR, CA, CH, CN, DE, DK, ES, GB, IL, JP, KE, LU, MX, NO, NZ, PT, RU, SE, SG, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9668870	A1	19980402	AU 1996-68870	19960913
CN 1230195	A	19990929	CN 1997-197816	19970910
PRIORITY APPLN. INFO.:			US 1996-25180	19960911
			WO 1996-IB945	19960913

AB Herein is described a specific amino acid sequence which exhibits specific ion (bridge) pair arrays enclosed on at least one side by non polar hydrophobic transmembrane segments, as a mechanism used by many infectious agents and a no. of cytokine inhibitory factors, such as interleukin 10 and prolactin inhibitory factor and alfa-fetoprotein, to not only undermine the hosts immune defences but to also allow for the infection of target lymphoid tissue. It has been demonstrated that certain vaccines, when inoculated into a host, produced a range of neutralizing antibodies but failed to prevent infection when that host is later challenged with live infectious organism. This present patent illustrates that when such vaccine inoculation is coupled with passive immunization with mono or polyclonal antibodies to these specific amino acid sequences as specified herein that the host is then capable of overcoming the infectious challenge. Herein is described the **therapeutic** use of mono or polyclonal antibodies to these said specific sequences as a **treatment** for acquired immune deficiency syndrome (AIDS) and other disease states that persist due to the presence of a cytokine inhibitory factor of viral, fungal, bacterial or host origin such as chronic fatigue syndrome where interleukin 10

mimic mols. are responsible for a multitude of disease symptoms identified as indicative of myalgic encephalitis. Herein is described the **therapeutic** use of mono or polyclonal antibodies to these specific amino acid sequences as a combination **therapy** with vaccines and anti-viral agents to prevent side effects from certain immune modulation and anti-viral agents (e.g. DHEA and **IL-12**) which cause enhanced prodn. of Interleukin 10 or AFP mimic mols. during **therapy**. Also herein is described the **therapeutic** use of these specific sequences either isolated from the organism source or produced by direct synthesis or recombinant protein synthesis. These peptides when **administered** to a patient suffering from an autoimmune disease, such as multiple sclerosis (MS), lupus (systemic lupus erythematosus) or diabetes or **rheumatoid arthritis** as limited examples or to transplant organ recipients, will allow the patient's immune state to be shifted to a Th2 antibody dependent immune response and curtail the Th1 (T cell dependent) immune attack which is evident in such immune malfunctions as MS and graft vs. host disease. Certain dermatol. conditions which are today **treated** by the use of corticosteroid creams and ointment may also be successfully **treated** by replacing the corticosteroid with these mimic immunosuppressive AFP/interleukin 10 sequences outlined in this patent.

L7 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:180782 CAPLUS
DOCUMENT NUMBER: 128:256389
TITLE: Immune direction **therapy**
INVENTOR(S): Prendergast, Patrick T.
PATENT ASSIGNEE(S): Prendergast, Patrick T., Ire.
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810787	A2	19980319	WO 1997-IB1086	19970910

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9741320 A1 19980402 AU 1997-41320 19970910
EP 929568 A2 19990721 EP 1997-939105 19970910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
CN 1230195 A 19990929 CN 1997-197816 19970910
SE 9900812 A 19990308 SE 1999-812 19990308
PRIORITY APPLN. INFO.: US 1996-25180 19960911
WO 1997-IB1086 19970910

AB Herein is described a specific amino acid sequence which exhibits specific ion (bridge) pair arrays enclosed on at least one side by non polar hydrophobic transmembrane segments, as a mechanism used by many infectious agents and a no. of cytokine inhibitory factors, such as interleukin 10 and prolactin inhibitory factor and alpha-fetoprotein, to not only undermine the hosts immune defences but to also allow for the infection of target lymphoid tissue. It has been demonstrated that certain vaccines, when inoculated into a host, produced a range of neutralizing antibodies but failed to prevent infection when that host is later challenged with live infectious organism. This present patent illustrates that when such vaccine inoculation is coupled with passive immunization with mono or polyclonal antibodies to these specific amino acid sequences as specified herein that the host is then capable of overcoming the infectious challenge. Herein is described the **therapeutic** use of mono or polyclonal antibodies to these said specific sequences as a **treatment** for acquired immune deficiency syndrome (AIDS) and other disease states that persist due to the presence of a cytokine inhibitory factor of viral, fungal, bacterial or host origin such as chronic fatigue syndrome where interleukin 10 mimic mols. are responsible for a multitude of disease symptoms identified as indicative of myalgic encephalitis. Herein is described the **therapeutic** use of mono or polyclonal antibodies to these specific amino acid sequences as a combination **therapy** with vaccines and anti-viral agents to prevent side effects from certain immune modulation and anti-viral agents (e.g. DHEA and **IL-12**) which cause enhanced prodn. of Interleukin 10 or AFP mimic mols. during **therapy**. Also herein is described the **therapeutic** use of these specific sequences either isolated from the organism source or produced by direct synthesis or recombinant protein synthesis. These peptides when **administered** to a patient suffering from an autoimmune disease, such as multiple sclerosis (MS), lupus (systemic lupus erythematosus) or diabetes or **rheumatoid arthritis** as limited examples or to transplant organ recipients, will allow the patient's immune state to be shifted to a Th2 antibody dependent immune response and curtail the Th1 (T cell dependent) immune attack which is evident in such immune malfunctions as MS and graft vs. host disease. Certain dermatol. conditions which are today **treated** by the use of

corticosteroid creams and ointment may also be successfully **treated** by replacing the corticosteroid with these mimic immunosuppressive AFP/interleukin 10 sequences outlined in this patent.

L7 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:12065 CAPLUS
DOCUMENT NUMBER: 128:149334
TITLE: Suppression of TNF-.alpha. expression, inhibition of Th1 activity, and amelioration of collagen-induced arthritis by rolipram
AUTHOR(S): Ross, Susan E.; Williams, Richard O.; Mason, Lesley J.; Mauri, Claudia; Marinova-Mutafchieva, Lilia; Malfait, Anne-Marie; Maini, Ravinder N.; Feldmann, Marc
CORPORATE SOURCE: Kennedy Institute Rheumatology, London, UK
SOURCE: J. Immunol. (1997), 159(12), 6253-6259
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rolipram is a type IV phosphodiesterase inhibitor that suppresses inflammation and TNF-.alpha. prodn. As anti-TNF-.alpha. **therapy** is effective in **rheumatoid arthritis**, we investigated the effect of rolipram on collagen-induced arthritis (CIA), a murine model of **rheumatoid arthritis**. Rolipram was **administered** after the onset of clin. arthritis at doses of 0.5, 3, 5, or 10 mg/kg twice daily, with a dose-dependent **therapeutic** effect on clin. severity and joint erosion. Immunohistochem. anal. of joints of rolipram-**treated** mice revealed 67% redn. in TNF-.alpha.-expressing cells compared with control arthritic mice. In vitro studies using bone marrow-derived macrophages confirmed that rolipram directly suppressed TNF-.alpha. and **IL-12** prodn. following stimulation with IFN-.gamma. and LPS. The effect of rolipram on T cell activity was studied by measuring Th1/Th2 cytokine prodn. by collagen-stimulated draining lymph node cells from arthritic mice **treated** in vivo with rolipram. Rolipram reduced IFN-.gamma. prodn. and increased IL-10, indicating that rolipram down-regulated the ongoing Th1 response to type II collagen. Finally, the effect on CIA of combination **therapy** was studied using rolipram plus either anti-TNF-.alpha. or anti-CD4 mAbs. Rolipram plus anti-TNF-.alpha. was not **therapeutically** additive, whereas rolipram plus anti-CD4 mAb was clearly additive. This result indicates that the **therapeutic** effects of rolipram overlap with TNF-.alpha. blockade, but are complementary to anti-CD4 **treatment**. It is therefore proposed that a major mechanism of action of rolipram in CIA is suppression of TNF-.alpha. activity. These findings

suggest that type IV phosphodiesterase inhibitors may be effective in pathol. conditions, such as **RA**, with overexpression of TNF-.alpha..

L7 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:777401 CAPLUS
DOCUMENT NUMBER: 128:60640
TITLE: Suppression of collagen-induced arthritis by continuous **administration** of IL-4
AUTHOR(S): Horsfall, Angela C.; Butler, Debra M.; Marinova, Lilia; Warden, Paul J.; Williams, Richard O.; Maini, Ravinder N.; Feldmann, Marc
CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, W6 8LH, UK
SOURCE: J. Immunol. (1997), 159(11), 5687-5696
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The onset of collagen-induced arthritis in DBA/1 mice is accompanied by a predominantly Th1 response, characterized by prodn. of the proinflammatory cytokines IFN-.gamma. and TNF-.alpha., and a predominance of IgG2a anti-collagen Abs. This study has primarily addressed the effects of continuous **administration** of exogenous IL-4, a Th2 cytokine, on collagen-induced arthritis in terms of time of onset, clin. symptoms, and histol. changes compared with those in untreated controls. The contributions of Th1 and Th2 cell responses were studied by examg. anti-CII IgG subclasses, serum IgE levels, and cytokine prodn. by synovial membrane and lymph node cell cultures. Continuous exposure to IL-4 for 28 days significantly delayed the onset of arthritis from 19 to 37 days and suppressed clin. symptoms. Arthritis occurred approx. 13 to 24 days after **treatment** ceased. Thereafter, the severity and duration of clin. symptoms were similar to those in control animals, although both joint damage and inflammation at the histol. and cellular levels were less severe than those in untreated controls. During IL-4 **treatment**, anti-collagen Ab levels were reduced (most significantly those of the IgG2a subclass), histol. scores were lower, and the most striking effect was a 1000-fold decrease in TNF-.alpha. secretion by synovial cells. No significant differences in IgE levels were found between controls and IL-4-**treated** mice. These data suggest that the anti-inflammatory properties of IL-4 are mediated in part by down-regulation of Th1 responses rather than up-regulation of Th2 responses.

L7 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:218678 CAPLUS
DOCUMENT NUMBER: 126:207517
TITLE: Nonionic surfactant vesicles as

therapeutic agents for **treatment** of inflammatory conditions and other conditions associated with elevated cytokine levels

INVENTOR(S): Roberts, Craig William; Brewer, James Macdonald; Alexander, James

PATENT ASSIGNEE(S): Proteus Molecular Design Limited, UK; Roberts, Craig William; Brewer, James Macdonald; Alexander, James

SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9704768	A1	19970213	WO 1996-GB1861	19960801
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
CA 2228298	AA	19970213	CA 1996-2228298	19960801
AU 9666262	A1	19970226	AU 1996-66262	19960801
AU 705662	B2	19990527		
EP 861074	A1	19980902	EP 1996-925904	19960801
R: BE, DE, ES, FR, GB, IT, NL, SE				
JP 11510155	T2	19990907	JP 1996-507372	19960801
PRIORITY APPLN. INFO.:			GB 1995-15868	19950802
			WO 1996-GB1861	19960801

AB A method is provided for **treating** or preventing inflammatory conditions and other conditions which are assocd. with elevated levels of cytokines. Such conditions include **rheumatoid arthritis** and asthmas. The method comprises **administering** nonionic surfactant vesicles (NISV) to the subject. NISV (contg. 1-monopalmitoyl glycerol, cholesterol, and dicetyl phosphate) reduced TNF-.alpha. levels in LPS-stimulated macrophages.

L7 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:756546 CAPLUS

DOCUMENT NUMBER: 126:17804

TITLE: Human antibodies derived from immunized xenomice

INVENTOR(S): Kucherlapati, Raju; Jakobovits, Aya; Klapholz, Sue; Brenner, Daniel G.; Capon, Daniel J.

PATENT ASSIGNEE(S): Cell Genesys, Inc., USA

SOURCE: PCT Int. Appl., 64 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9634096	A1	19961031	WO 1995-US5500	19950428
W: AU, CA, FI, HU, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2219486	AA	19961031	CA 1995-2219486	19950428
AU 9524668	A1	19961118	AU 1995-24668	19950428
EP 823941	A1	19980218	EP 1995-918935	19950428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 11505107	T2	19990518	JP 1995-532463	19950428
PRIORITY APPLN. INFO.:			WO 1995-US5500	19950428

AB Antibodies with fully human variable regions against a specific antigen can be prepd. by **administering** the antigen to a transgenic animal which has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled. Various subsequent manipulations can be performed to obtain either antibodies per se or analogs thereof.

L7 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:557675 CAPLUS
DOCUMENT NUMBER: 125:273338
TITLE: Application of **interleukin 12** to antitumor cytokine and gene **therapy**
AUTHOR(S): Nishimura, Takashi; Watanabe, Kazuhito; Yahata, Takashi; Ushaku, Lee; Ando, Kiyoshi; Kimura, Minoru; Saiki, Ikuo; Uede, Toshimitsu; Habu, Sonoko
CORPORATE SOURCE: Sch. Med., Tokai University, Isehara, 259, Japan
SOURCE: Cancer Chemother. Pharmacol. (1996), 38(Suppl.), S27-S34
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Administration** of **interleukin 12** (**IL-12**) in vivo at 2000 U/mouse induced **IL-12**-activated killer (IL-12AK) cells and elevated serum interferon-.gamma. (IFN-.gamma.) activity. Beside NK1.11+CD3- natural killer cells, asialoGM1+CD8+ T-cells were shown as novel precursors. **IL-12** was effective in inducing tumor-specific cytotoxic T-lymphocytes, in preventing, and inhibiting the growth of primary tumors induced by methylnitrosourea

in c-Ha-**ras** transgeneic mice. The transfer of the **IL-12** gene into A20 B-lymphoma cells resulted in continuous prodn. of **IL-12** and caused abrogation of in vivo tumorigenicity. Tumor cells transfected with the **IL-12** gene induced IL-12AK cells, IFN-.gamma. prodn., and tumor-specific protective immunity. B16-BL-6 melanoma cells showed resistance to **IL-12** gene **therapy**, combination **therapy** with the B7-1 gene and systemic **IL-12 administration** inhibited tumor metastasis. Using B16-BL-6 melanoma cells transfected with B7-1 and **IL-12** genes, similar results were obtained, suggesting **IL-12** as a cytokine for antitumor cytokine and gene **therapy**.

L7 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:934127 CAPLUS
DOCUMENT NUMBER: 123:337469
TITLE: Use of **IL-12** and **IL-12** antagonists in **treatment** of autoimmune diseases
INVENTOR(S): Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9524918	A1	19950921	WO 1995-US2550	19950307
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
ZA 9500960	A	19951010	ZA 1995-960	19950207
CA 2185565	AA	19950921	CA 1995-2185565	19950307
AU 9519749	A1	19951003	AU 1995-19749	19950307
AU 689236	B2	19980326		
EP 750509	A1	19970102	EP 1995-912666	19950307
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09510444	T2	19971021	JP 1995-524044	19950307
PRIORITY APPLN. INFO.:			US 1994-212629	19940314
			WO 1995-US2550	19950307

AB Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, **rheumatoid arthritis**, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune

thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are **treated** in mammals by **administering IL-12** or an **IL-12** antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with **IL-12** during restimulation, and alleviated by injection of a polyclonal antibody to **IL-12**.

L7 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:97212 CAPLUS
DOCUMENT NUMBER: 120:97212
TITLE: Ligand for the c-kit receptor and methods of use thereof
INVENTOR(S): Besmer, Peter; Buck, Jochen; Moore, Malcolm A. S.; Nocka, Karl
PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 215 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9321936	A1	19931111	WO 1993-US3640	19930416
W: AU, CA, HU, JP, KR, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9341065	A1	19931129	AU 1993-41065	19930416
AU 675429	B2	19970206		
EP 639979	A1	19950301	EP 1993-910645	19930416
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07508721	T2	19950928	JP 1993-519322	19930416
HU 70696	A2	19951030	HU 1994-3054	19930416
US 6001803	A	19991214	US 1994-325240	19941020
US 5767074	A	19980616	US 1994-341456	19941117
PRIORITY APPLN. INFO.:			US 1992-873962	19920423
			US 1990-573483	19900827
			US 1990-594306	19901005
			WO 1993-US3640	19930416

AB A pharmaceutical compn. which comprises purified or recombinant

c-kit ligand (KL) in combination with other hematopoietic factors and a pharmaceutically acceptable carrier is provided as well as methods of **treating** patients which comprise **administering** to the patient the pharmaceutical compn. of this invention. This invention provides combination **therapies** using KL and a KL polypeptide, or a sol. fragment thereof and other hematopoietic factors. It also provides methods and compns. for ex-vivo use of KL alone or in combination **therapy**. A mutated KL antagonist is also described. Such an antagonist may also be a small mol. Antisense nucleic acids to KL as **therapeutics** are also described. Lastly, compns. and methods are described that take advantage of the role of KL in germ cells, mast cells and melanocytes. KL was purified from mouse fibroblast conditioned medium and cDNA was isolated and sequenced. The interactions of IL-1, IL-6, and KL on primitive murine progenitor cell compartments were studied. There were synergistic and additive effects of these factors alone or in conjunction with CSFs. IL-1, IL-6, and KL stimulate early hematopoiesis.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:03:12 ON 06 MAR 2001)

L10 83 SEA ABB=ON PLU=ON L4 AND (TREAT? OR THERAP?)(5A)(RA OR RHEUMAT? ARTHRIT?)
L11 20 SEA ABB=ON PLU=ON L10 AND ADMIN?
L12 16 DUP REM L11 (4 DUPLICATES REMOVED)

L12 ANSWER 1 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-102680 [11] WPIDS
DOC. NO. CPI: C2001-030059
TITLE: New morpholinyl triazine derivatives, useful as **interleukin-12** inhibitors for treating e.g. sepsis and autoimmune disorders such as rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis.
DERWENT CLASS: B02 B03
INVENTOR(S): BRUNKHORST, B; ONO, M; VO, N H; WADA, Y; WARCHOL, T; WRONA, W; ZHOU, D
PATENT ASSIGNEE(S): (SHIO) SHIONOGI BIORESEARCH CORP
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000078757	A1	20001228	(200111)*	EN	45

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU

SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000078757 A1		WO 2000-US16094	20000612

PRIORITY APPLN. INFO: US 1999-139623 19990617
AN 2001-102680 [11] WPIDS
AB WO 200078757 A UPAB: 20010224
NOVELTY - Morpholinyl triazine derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Morpholinyl triazine derivatives of formula (I) and their salts are new.

X = triazinyl;

L1 = A1-B1;

A1-= (CH(Ra))m, O, S or N(Rb);

B1 = (CH(Rc))n or a bond;

Ra, Rc = H, alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;

Rb = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;

m, n = 1-8;

W = cycloalkyl, heterocycloalkyl, aryl or heteroaryl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl or alkylcarbonyloxy;

L2 = A2-B2

A2 = a bond, N(R1) or (C(R2)(R3))p;

B2 = a bond, N=C(R4), C(R5)=N, C(R6)=C(R7), N(R8)=N(R9), N(R10)C(R11)(R12), OC(R13)(R14), COC(R15)(R16), CON(R17), N(R18)CO, CO, COO, COS, SC(R19)(R20), CS-C(R21)(R22), CS-N(R23), N(R24)CS, CS or SO2; or

A2-B2 = O, S, (O(CH2)qO)r, (N(R25)(CH2)sCO)t or (N(R26)(CH2)uN(R27))v;

provided that A2-B2 is not a bond;

R1-R27 = H, alkyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

p, q, r, s, t, u, v =.1-3;

Y = R'-L'-R'';

L' = a bond, O, S, N(R28), N(R29)CO, CON(R30), COO or OCO;

R28-R30 = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;

R' = a bond, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy or alkoxycarbonylimino;

R'' = cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, or alkylcarbonyloxy;

Z = morpholinyl optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo; haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl or alkylcarbonyloxy.

ACTIVITY - Antiinflammatory; antirheumatic; antiarthritic; antipsoriatic; antibacterial; immunosuppressive; neuroprotective.

MECHANISM OF ACTION - Inhibitor of interleukin (**IL**)-**12** production (claimed).

Using mononuclear cells from human peripheral blood (PBMC), a number of tested compounds (I) (unspecified) demonstrated over 70% inhibition of **IL-12** compared to control. In a specificity assay, the 2 most potent compounds (I) (out of 9, all unspecified), exhibited a 10-fold increase in inhibiting **IL-12** production over a known anti-inflammatory compound, dexamethazone.

USE - For inhibiting **IL-12** production or treating **IL-12** mediated disorders including sepsis and autoimmune disorders e.g. rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis. Prior art in vivo studies also revealed that inhibition of **IL-12** production has therapeutic effects against inflammatory disorders such as collagen induced arthritis, established colitis, experimental autoimmune encephalomyelitis, experimental autoimmune uveoretinitis and cyclophosphamide induced diabetes. (I) may be used in conjunction with other therapeutic agents, e.g. antiinflammatory agents.

In an animal study using Balb/c mice in which septic shock had been induced by single intradermal injection of LPS (1 mu g/ml) in the foot pad, 3 tested compounds (I) (unspecified) **administered** at 10-20 mg/kg/day for 3 days produced a survival rate of 60% and 80% in 2/5 groups, whilst all mice died in the groups that received no treatment or vehicle only.

ADVANTAGE - (I) are small non-protein compounds (cf. anti-**IL-12** antibodies which can be unstable after

administration and whose use in long term treatments of chronic diseases is expensive). Also, in a cytotoxicity assay, 4 out of 9 tested compounds (I) showed a lower cytotoxicity toward PBMC cell line compared to dexamethazone, and 3 (out of the same 9 compounds (I)) showed a lower cytotoxicity toward THP-1 cell line compared to dexamethazone.
Dwg.0/0

L12 ANSWER 2 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-007004 [01] WPIDS
DOC. NO. CPI: C2001-001678
TITLE: Use of early T lymphocyte activation-1/osteopontin modulators for modulating a type-1 immune response in humans for treating cancer, AIDS, allergy, bacterial arthritis, granulomatous disorder, glomerulonephritis.
DERWENT CLASS: B04
INVENTOR(S): ASHKAR, S; CANTOR, H; GLIMCHER, M; WEBER, G
PATENT ASSIGNEE(S): (CHIL-N) CHILDRENS MEDICAL CENT; (DAND) DANA FARBER CANCER INST INC
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000063241	A2	20001026	(200101)*	EN	120
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000043575	A	20001102	(200107)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000063241	A2	WO 2000-US10340	20000417
AU 2000043575	A	AU 2000-43575	20000417

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000043575	A Based on	WO 200063241

PRIORITY APPLN. INFO: US 1999-129772 19990415
Searcher : Shears 308-4994

AN 2001-007004 [01] WPIDS
AB WO 200063241 A UPAB: 20001230
NOVELTY - Use of Eta (early T lymphocyte activation)-1/osteopontin (Opn) modulators for modulating a type-1 immune response in a subject.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) enhancing (M1) production of type-1 immune response associated cytokine by an immune cell, involves contacting the cell with an Eta-1/Opn stimulatory modulator;

(2) down regulating (M2) production of a type-2 immune response associated cytokine by an immune cell, involves **administering** a Eta-1/Opn inhibitory modulator;

(3) stimulating (M3) IL(**interleukin**)-**12** production or inhibiting IL-10 production by a macrophage, involves contacting the macrophage with Eta-1/Opn stimulatory modulator or Eta-1/Opn inhibitory modulator, respectively;

(4) modified tumor cells comprising irradiated tumor cells transduced with Eta-1/Opn;

(5) a biosynthetic immunomodulatory molecule (I) comprising a **IL-12** stimulatory component or IL-10 inhibitory component, and a first biomodular component, forming a molecule which modulates an immune response;

(6) a biosynthetic immunomodulatory molecule comprising a **IL-12** stimulatory component or IL-10 inhibitory component, a calcium/apatite binding domain and a heparin domain;

(7) an isolated nucleic acid molecule (II) comprising nucleic acid sequences which encode the above mentioned immunomodulatory molecules;

(8) an expression vector (III) comprising (II);

(9) a host cell (IV) comprising (III);

(10) producing (I) which involves culturing (IV) under conditions such that (I) is produced; and

(11) a pharmaceutical composition comprising (I).

ACTIVITY - Antibacterial; virucide; antiparasitic; antifungal; cytostatic; anti-HIV; antiallergic; immunomodulator; antibacterial; immunosuppressive; antiarthritic; antirheumatic; neuroprotective; nephrotropic; ophthalmological; antitumor; vulnerary.

MECHANISM OF ACTION - Type-1 or type-2 immune response modulator i.e. by modulating **IL-12** and IL-10 production by immune cells; gene therapy. The biological activity of Eta-1/Opn was tested in mice. Eta-1-/- mice were infected in the right eye with 4 multiply 106 plaque forming units (PFU) herpes simplex virus type-1 (HSV-1) (KOS strain) and challenged five days later in the left footpad with 1 multiply 105 PFU of UV-inactivated HSV-1 (KOS). Eta-1-/- (Opn-/-) mice infected by HSV-1(4 multiply 106 PFU via the cornea) fail to develop a significant delayed type hypersensitivity (DTH) response after footpad challenge with 105 pfu HSV-1 in contrast to the strong DTH response of Eta-1+/+(Opn+/+)

controls. Eta-1-/- and control mice (Eta-1+/+) were subjected to ocular challenge with virus. Eta-1-/- mice failed to develop significant HSK within 2 weeks after corneal inoculation with HSV-1 in contrast to the severe HSK developed within this period by control littermates (Eta-1+/+) (i.e. 65% of control Eta-1+/+ mice developed herpes simplex keratitis (HSK). Similar results were obtained when the experiment was repeated using BALB/cB gamma J mice and CB-17 mice in addition to Eta-1-/- and Eta-1+/+ mice. Furthermore skewing of the cell numbers in Eta-1/Opn knockout mice after challenge with HSV-1 was diminished compared to control mice in which the increase of CD8+ cells is consistent with a Th-1 response. Although cells from the draining lymph nodes of virus-infected Eta-1-/- and Eta-1+/+ mice respond equally well to HSV-1 according to (3H)-thymidine incorporation after viral restimulation in vitro, they differed conspicuously according to their cytokine profiles. Cells were isolated and restimulated with HSV-1 (KOS) as described above. Supernatants were harvested 48 h later and IL-10 and **IL-12** p40 cytokine levels were measured by sandwich ELISA using OptIEA antibody sets. IL-4 was measured after stimulation of draining lymph node cells by plate-bound anti-CD3. Cells from Eta-1-/- mice produced high levels of IL-10 and IL-4 but markedly reduced levels of **IL-12** compared with Eta-1-/- controls. Splenic macrophages from virus-infected Eta-1+/+ but not Eta-1-/- mice continued to produce **IL-12** ten days after infection. In contrast with the sterile granulomatous response. IFN- gamma levels were not reduced in Eta-1-/- mice after HSV-1 viral function, consistent with an **IL-12**-independent pathway to IFN- gamma production that may depend on virally induced IFN- alpha / beta production. Moreover expression of IL-2 by lymph node and spleen T lymphocytes from Eta-1-/- and Eta-1+/+ littermates in response to immobilized antibody to CD3 was indistinguishable between the C57BL/6 multiply 129/SV Eta-1-/- and C57BL/6 multiply Eta-1+/+ mice. These cytokine profiles suggest that Eta-1/Opn expression normally may imprint the in vivo ratio of **IL-12** and IL-10 cytokines that dictates a type-1 immunity.

USE - For potentiating a type-1 immune response in a subject which involves culturing immune effector cells from a subject in the presence of Eta-1/Opn stimulatory modulator and then **administering** the cultured cells to the subject such that type-1 immune response is potentiated. Eta-1/Opn stimulatory modulators are useful for treating burn-associated sepsis, bacterial infection, viral infection, parasitic infection, mycoplasma infection, fungal infection, cancer, immunodeficiency disorders, AIDS, bone marrow transplant-related immunodeficiency, chemotherapy-related immunodeficiency and allergy. The Eta-1/Opn inhibitory modulators are useful for **treating** bacterial arthritis, granulomatous disorder, glomerulonephritis, **rheumatoid arthritis**, multiple sclerosis, herpes

simplex keratitis, and autoimmune disease. (I) is used for modulating an immune response which involves modulating cytokine secretion, chemotaxis regulation, regulation of hapotaxis, and regulation of cell spreading (claimed). (I) is useful in biasing an immune response towards a delayed type hypersensitivity (DTH) response i.e., towards type-1 immunity. It is also useful for wound healing, enhancement of the immune response and in treatment of granulomatous disease. The nucleic acids encoding (I) are useful in gene therapy techniques for treating the above mentioned disorders. Dwg.0/14

L12 ANSWER 3 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-422868 [36] WPIDS
CROSS REFERENCE: 1996-268530 [27]; 1998-377241 [29]; 2000-061893 [05]; 2000-071668 [05]; 2000-170770 [05]
DOC. NO. CPI: C2000-127890
TITLE: Therapeutic treatment of for example viral diseases such as chronic hepatitis B and C, cancers such as leukemia, and multiple sclerosis comprises **administering** an immunological tolerance inducing compound prior to an effective drug .
DERWENT CLASS: B04 D16
INVENTOR(S): TOVEY, M G
PATENT ASSIGNEE(S): (PHAR-N) PHARMA PACIFIC PTY LTD
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000032223	A2	20000608	(200036)*	EN	26
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU JP US					
AU 2000013991	A	20000619	(200044)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000032223	A2	WO 1999-GB4009	19991201
AU 2000013991	A	AU 2000-13991	19991201

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000013991	A Based on	WO 200032223

PRIORITY APPLN. INFO: EP 1998-403020 19981202
AN 2000-422868 [36] WPIDS
Searcher : Shears 308-4994

CR 1996-268530 [27]; 1998-377241 [29]; 2000-061893 [05]; 2000-071668 [05]; 2000-170770 [05]

AB WO 200032223 A UPAB: 20000801

NOVELTY - Therapeutic treatment of a subject with an immunogenic drug comprising:

(a) **administering** oromucosally a first formulation comprising a compound which induces immunological tolerance to the drug; and

(b) **administering** a second formulation comprising the drug that effects the therapeutic treatment.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) A kit for therapeutic treatment of a subject with an immunogenic drug comprising a formulation comprising a compound to induce immunological tolerance to the drug and a formulation comprising the drug to effect the therapeutic treatment;

(2) Using an immunogenic drug for the manufacture of a formulation to effect therapeutic treatment of a disease of a human or animal which has become immunologically tolerant to the drug by the oromucosal route of a formulation comprising a compound that induces immunological tolerance; and

(3) Using a compound for the manufacture of a formulation for oromucosal **administration** to a human or animal to induce immunological tolerance to an immunological drug where the human or animal is also **administered** a second formulation comprising the drug to effect a therapeutic effect.

ACTIVITY - Virucide; Cytostatic; Neuroprotective; Immunostimulant; Antianemic; Antibacterial; Immunosuppressive; Antirheumatic; Antiarthritic.

MECHANISM OF ACTION - None given.

USE - For therapeutic treatment of a human or animal. An immunogenic drug or compound is used to manufacture formulations for inducing an immunological tolerance or effecting therapeutic treatment (claimed). Viral diseases, such as chronic hepatitis B and C, herpes, and influenza; cancers, such as leukemia, lymphomas and solid tumors; and multiple sclerosis are treated. Neutropenia and leukopenia following chemotherapy are treated. Anemia, chronic renal failure. septic shock and **rheumatoid arthritis** are **treated**. Cystic fibrosis and Gaucher disease can be treated by gene therapy.

ADVANTAGE - An immunological tolerance to an immunogenic drug is induced so that when the drug is subsequently **administered**, its pharmacokinetics and/or clinical effectiveness are improved. Rejection of drugs that are **administered** in repeat doses over a period of time by the immune system is less likely. The amount of drug that needs to be **administered** is reduced, lowering costs. Non-humanized antibodies that cannot normally be used for therapy due to rejection by the immune system can be used.

Dwg.0/0

L12 ANSWER 4 OF 16 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:940812 SCISEARCH
THE GENUINE ARTICLE: 381HX
TITLE: All-trans-retinoic acid and polyriboinosinoic: polyribocytidylic acid cooperate to elevate anti-tetanus immunoglobulin G and immunoglobulin M responses in vitamin A-deficient Lewis rats and Balb/c mice
AUTHOR: DeCicco K L; Ross A C (Reprint)
CORPORATE SOURCE: PENN STATE UNIV, DEPT NUTR, UNIVERSITY PK, PA 16802 (Reprint); PENN STATE UNIV, DEPT NUTR, UNIVERSITY PK, PA 16802; PENN STATE UNIV, GRAD PROGRAM NUTR, UNIVERSITY PK, PA 16802
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NUTRITION SOCIETY, (NOV 2000) Vol. 59, No. 4, pp. 519-529.
Publisher: C A B INTERNATIONAL, C/O PUBLISHING DIVISION, WALLINGFORD OX10 8DE, OXON, ENGLAND.
ISSN: 0029-6651.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 62

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vitamin A (VA) deficiency compromises antibody responses to T-cell-dependent antigens such as tetanus toroid, but this effect can be reversed through **administration** of retinol or retinoic acid (RA). To test whether RA and polyriboinosinioc : polyribocytidylic acid (PIC), a known inducer of several forms of interferon (IFN), can cooperate to increase specific immunoglobulin (Ig)G and IgM production during VA deficiency, rats and mice were made VA-deficient, immunized with TT and **treated** with all-trans-**RA**, PIC or their combination. VA-deficient rats produced low primary and secondary anti-tetanus IgG responses (VA-deficient controls v. VA-sufficient controls $P < 0.001$), although total IgG was slightly elevated when compared with VA-sufficient control rats. Although RA **administered** alone elevated antibody production during VA deficiency to control levels, RA combined with PIC synergistically enhanced these responses (RA and PIC group v. all other groups $P<0.0001$). In contrast, Balb/c mice maintained on a VA-deficient diet and immunized in a similar fashion showed no impairment in antigen-specific IgG levels, but **treatment** with a combination of **RA** and PIC still evoked an additive enhancement in antigen-specific antibody production. Additionally, R4 and PIC **administration** to VA-sufficient mice resulted in elevated antibody responses, suggesting that this combination should be evaluated further for its

immune-stimulatory effects.

L12 ANSWER 5 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000214197 EMBASE
TITLE: Rheumatoid arthritis exacerbation caused by exogenous **interleukin-12**.
AUTHOR: Peeva E.; Fishman A.D.; Goddard G.; Wadler S.; Barland P.
CORPORATE SOURCE: Dr. P. Barland, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, United States
SOURCE: Arthritis and Rheumatism, (2000) 43/2 (461-463).
Refs: 14
ISSN: 0004-3591 CODEN: ARHEAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Interleukin-12** (**IL-12**) is a pleiotropic cytokine with proinflammatory, immunoregulatory, antitumor, and antimetastatic properties. It plays a crucial role in the development of the Th1 response and subsequent interferon-.gamma., production and enhancement of cell-mediated cytotoxicity. Recently, **IL-12** has been used as an experimental therapy for cancer. Given the multiple immunomodulatory properties of **IL-12**, there are potential concerns associated with its clinical use. Of special interest are the possible side effects of **IL-12** therapy in patients with autoimmune diseases, especially those that are T cell mediated, such as rheumatoid arthritis (RA). We present a case of severe **RA** exacerbation caused by **treatment** with **IL-12** for metastatic cervical cancer. This is the first reported case of RA flare caused by exogenous **IL-12**.

L12 ANSWER 6 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000323125 EMBASE
TITLE: Retinoic acid and polyriboinosinic acid act synergistically to enhance the antibody response to tetanus toxoid during vitamin a deficiency: Possible involvement of interleukin-2 receptor-.beta., signal transducer and activator of transcription-1, and interferon regulatory factor-1.
AUTHOR: Decicco K.L.; Zolfaghari R.; Li N.-Q.; Ross A.C.
CORPORATE SOURCE: Dr. A.C. Ross, Nutrition Dept., 126-S Henderson Bldg., University Park, PA 16802, United States.
Searcher : Shears 308-4994

acr6@psu.edu
SOURCE: Journal of Infectious Diseases, (2000) 182/3 SUPPL. 1 (S29-S36).
Refs: 60
ISSN: 0022-1899 CODEN: JIDIAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Antibody responses to T cell-dependent antigens are reduced during vitamin A (VA) deficiency and restored by retinoids. To test whether retinoic acid (RA) and polyinosinic:polycytidylic acid (PIC), an inducer of interferons, can increase specific antibody production, VA-deficient rats were **treated** with all-trans-**RA**
, PIC, or both at the time of primary immunization with tetanus toxoid. VA-deficient rats produced low primary and secondary anti-tetanus IgG responses (P < .001 vs. VA-sufficient controls). Both responses were increased synergistically by RA plus PIC (P < .0001). In VA-deficient spleens, mRNAs were low for interleuldn (IL)-2 receptor-.beta., interferon regulatory factor-1, and signal transducer and activator of transcription 1. Each, however, was induced by RA plus PIC (P < .0001 vs. controls). Conversely, **IL-12** and IL-10 mRNAs were elevated in VA deficiency and were induced by PIC and suppressed by RA. Thus, RA plus PIC appears to be a promising combination for stimulating antigen-specific immunity. Several molecular factors identified here may partially account for the observed enhancement.

L12 ANSWER 7 OF 16 MEDLINE
ACCESSION NUMBER: 2000232262 MEDLINE
DOCUMENT NUMBER: 20232262
TITLE: [Osteoporosis in rheumatoid arthritis--significance of alfacalcidol in prevention and therapy]. Osteoporose bei rheumatoider Arthritis--Bedeutung von Alfacalcidol in Pravention und Therapie.
AUTHOR: Schacht E
SOURCE: ZEITSCHRIFT FUR RHEUMATOLOGIE, (2000) 59 Suppl 1 10-20. Ref: 50
Journal code: Y0V. ISSN: 0340-1855.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: German
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200007
ENTRY WEEK: 20000703

AB Besides localised osteopenia, patients with rheumatoid arthritis (RA) with or without corticosteroids develop in 30-50% osteoporosis induced by several factors and thus a higher risk of fractures. Bone loss appears very early and correlates directly with disease activity and also later with the negative effects of restrictive mobility. Corticosteroids reduce as a pathogenetic co-factor intestinal calcium absorption and increase renal calcium excretion resulting in compensatory increased PTH-release and increased sensitivity of bone to PTH. In addition, corticosteroids inhibit osteoblast function as well as the favourable effects of growth factors and sex hormones on bone. It has recently been recognised that the expression of D-hormone receptors (VDRs) is suppressed by these medications and that corticosteroids probably induce VDR disorders. The negative influence of corticosteroids on muscle strength (indirectly--via increased PTH-levels, lowered IGF-1-levels or reduced D-hormone activity) is a feature which has been underestimated. The demonstrated drop in 1,25(OH)2D3 (D-hormone) levels in patients with RA in correlation with C-reactive protein (CRP) is of significance in the pathogenesis of RA-induced osteoporosis and could further promote the process of inflammation. There is a general consensus that cytokines (e.g. IL-1, IL-6, **IL-12**, TNF-alpha) induce bone resorption in inflammatory rheumatic diseases. There are, however, new findings which show that cytokines like TNF-alpha also interfere with bone formation by promoting apoptosis of osteoblasts and reduce the muscle strength, too. D-hormone preparations (alfacalcidol, calcitriol) possess immunoregulatory effects in vitro and in vivo by inhibiting the cytokines IL-1, IL-6, TNF-alpha and particularly **IL-12**. At the cellular level, D-hormone reduces the expression of Th1 helper cells directly or indirectly by inhibition of **IL-12** from monocytes. Therapy with alfacalcidol or calcitriol results in increased production of Th2 helper cells which produce bone protective cytokines like IL-4 and IL-10. It is important to know that D-hormone protects osteoblasts against TNF-alpha-induced cell death. After conversion to D-hormone in the liver and bone, alfacalcidol antagonises the above described pathogenetic factors of the corticosteroids. D-hormone is one of the body's own immunoregulators, which is produced in macrophages in cases of need to reduce immunological overreactions in a feed-back loop. Improved understanding of the pathogenesis of corticosteroid-induced osteoporosis and of the pharmacological effects of alfacalcidol in this type of iatrogenic bone loss as well as the results of specific animal models simulating bone loss in inflammatory diseases explain the favourable effects of alfacalcidol in this indication. Various clinical studies have demonstrated clearly that alfacalcidol retards corticosteroid-induced bone loss in contrast to plain vitamin D. Due to its immunomodulating

properties, alfacalcidol is particularly suitable for RA-induced bone loss and for the prevention of transplantation osteoporosis, and an adjuvant contribution to the disease-modifying **therapy** of **RA** and to the immunosuppressive **therapy** after transplantation can not be excluded.

L12 ANSWER 8 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-038737 [03] WPIDS
DOC. NO. CPI: C2000-009915
TITLE: Enhancing IL-10 production by cells expressing Fc-gamma RI receptors, useful in treatment of endotoxemic shock or autoimmune disease.
DERWENT CLASS: B04
INVENTOR(S): MOSSER, D M; SUTTERWALA, F S
PATENT ASSIGNEE(S): (UTEM) UNIV TEMPLE
COUNTRY COUNT: 85
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9956777	A1	19991111	(200003)*	EN	52

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9938710	A	19991123	(200016)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9956777	A1	WO 1999-US9269	19990429
AU 9938710	A	AU 1999-38710	19990429

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9938710	A	Based on	WO 9956777

PRIORITY APPLN. INFO: US 1998-84385 19980506
AN 2000-038737 [03] WPIDS
AB WO 9956777 A UPAB: 20000118
NOVELTY - Enhancement of interleukin-10 (IL-10) production by Fc gamma RI receptor expressing mammalian cells involves **administration** of an agent (I) which (alone or in combination with one or more substances in the body) causes ligation

of such receptors on the cells.

ACTIVITY - Immunosuppressive; antibacterial; antirheumatic; antiarthritic; antianemic.

MECHANISM OF ACTION - Fc gamma RI receptor ligation; IL-10 production stimulation; **IL-12** biosynthesis suppressant.

Ligation of the Fc gamma RI receptor selectively upregulates production of IL-10 (an inhibitor of T(H)1 type immune response), which in turn markedly suppresses cellular biosynthesis of **IL-12** (a potent inducer of cell-mediated immune response), especially in macrophages. RAG-1-/- mice were each treated intravenously with 4 mu g of lipopolysaccharide (LPS) or IgG opsonized LPS. Analysis of serum samples 3 hours post-challenge showed that the IL-10 and **IL-12** p40 levels were ca. 120 pg/ml and 35 pg/ml respectively using LPS, compared with ca. 330 pg/ml and 10 pg/ml respectively using the IgG opsonized LPS.

USE - For inhibiting a proinflammatory immune response, especially for preventing or treating shock associated with bacterial endotoxemia or **treating** autoimmune disease, specifically Kawasaki disease, **rheumatoid arthritis**, inflammatory bowel disease, Sydenham's chorea, autoimmune hemolytic anemia or particularly systemic lupus erythematosus (all claimed). More generally, macrophage proinflammatory responses to infectious and/or inflammatory stimuli are suppressed.

Dwg.0/10

L12 ANSWER 9 OF 16 MEDLINE

ACCESSION NUMBER: 1999354937 MEDLINE

DOCUMENT NUMBER: 99354937

TITLE: Anti-**IL-12** and anti-TNF antibodies synergistically suppress the progression of murine collagen-induced arthritis.

AUTHOR: Butler D M; Malfait A M; Maini R N; Brennan F M; Feldmann M

CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, GB.

SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jul) 29 (7) 2205-12.
Journal code: EN5. ISSN: 0014-2980.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199910

ENTRY WEEK: 19991002

AB The co-ordinate role of the Th1 cytokine **IL-12** and the proinflammatory cytokine TNF in arthritis was explored using the DBA/1 mouse model, collagen-induced arthritis (CIA). In this study, mice with established arthritis were treated with anti-

IL-12 and/or anti-TNF antibodies for 10 days from the onset of disease. Clinical assessment showed that the combined antibody treatment ameliorated disease severity to a greater extent than anti-TNF alone. Supporting these observations, histological analysis revealed that there was a reduced joint damage in the mice that received combined anti-**IL-12** and anti-TNF treatment, compared to the other treatment groups. Anti-**IL-12** had no statistically significant effect on the clinical outcome of disease. The combination of anti-**IL-12** and anti-TNF treatment was found to reduce collagen type II (CII)-specific lymph node cell IFN-gamma production and proliferation, as well as decrease the anti-CII IgG2a:IgG1 ratio more effectively than either treatment alone. When the antibodies were added to synovial cells from arthritic mice and bone marrow macrophages in vitro, anti-TNF diminished **IL-12** production, but anti-**IL-12** had no effect on TNF production. These data suggest that, through the partial regulation of **IL-12**, TNF modulates the immune response in arthritis, as well as the inflammatory response. The synergistic action of anti-TNF and anti-**IL-12** on CIA may provide a new **therapeutic** approach for **treating rheumatoid arthritis**.

L12 ANSWER 10 OF 16 MEDLINE
ACCESSION NUMBER: 2000114114 MEDLINE
DOCUMENT NUMBER: 20114114
TITLE: [Collagen in the treatment of rheumatic diseases--oral tolerance].
Kolagen v liecbe reumatickych chorob--oralna tolerancia.
AUTHOR: Stancikova M; Stancik R; Gubzova Z; Rovensky J
CORPORATE SOURCE: Research Institute of Rheumatic Diseases, Piestany, Slovakia.. stancikova@vurch.sk
SOURCE: BRATISLAVSKE LEKARSKE LISTY, (1999) 100 (10) 567-71.
Journal code: B5N. ISSN: 0006-9248.
PUB. COUNTRY: Slovakia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Slovak
ENTRY MONTH: 200004
ENTRY WEEK: 20000402
AB The term "oral tolerance" means antigen specific suppression of immune response after oral application of antigen. Primary mechanisms by which oral tolerance is mediated include: deletion, anergy and active cellular suppression. The determining factor in this process is the dose of applied antigen. High doses of antigen develop deletion and anergy of cells while low doses of antigen result in bystander suppression. Recently bystander suppression has attracted attention in the treatment of autoimmune diseases. This process is connected with induction of regulatory T cells of Th2/Th3

phenotypes in gut with characteristic profile of anti-inflammatory cytokines as IL-4, IL-10 and TGF-beta. By means of circulation the lymphocytes enter the affected place and when meeting again with the antigen, they produce the same profile of cytokines which they originally made in the gut. These cytokines then suppress local autoimmune and inflammatory reaction independently of the antigen type. After successful trials of treatment with low doses of orally applied collagen type II in animal models of experimental arthritis, this treatment was also studied in clinical trials in humans with rheumatoid arthritis. Although the results obtained to this date are very promising they can not be considered final. Several questions still need to be solved: identification of responders, determination of character and amount of collagen applied as well as the route of application. Another promising therapeutic approach could be the simultaneous application of collagen and the compounds enhancing the cell response of Th2 or Th3 lymphocytes such as TGF-beta, IL-2, antibodies to **IL-12** which can augment the oral tolerance. In clinical praxis the treatment of osteoarthrosis with collagen type I has also been successfully applied. Induction of oral tolerance is new approach in the **treatment** of **rheumatoid arthritis** and as each new **therapy**, it requires refinement. In the future it is expected that an improved study design and a better understanding of the underlying mechanisms of oral tolerance will lead to an increased efficacy of the therapy in humans similar to the effectiveness previously demonstrated in animal models.

L12 ANSWER 11 OF 16 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999116747 MEDLINE
DOCUMENT NUMBER: 99116747
TITLE: Amelioration of collagen-induced arthritis and suppression of interferon-gamma, **interleukin -12**, and tumor necrosis factor alpha production by interferon-beta gene therapy.
AUTHOR: Triantaphyllopoulos K A; Williams R O; Tailor H; Chernajovsky Y
CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, UK.
SOURCE: ARTHRITIS AND RHEUMATISM, (1999 Jan) 42 (1) 90-9. Journal code: 90M. ISSN: 0004-3591.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY WEEK: 19990401
AB OBJECTIVE: To investigate the therapeutic effects and possible mechanisms of action of constitutive expression of interferon-beta (IFNbeta) by syngeneic fibroblasts from DBA/1 mice in the collagen-induced arthritis (CIA) model. METHODS: Immortalized

embryonic DBA/1 fibroblasts were infected with a retrovirus expressing murine IFNbeta. IFNbeta-expressing fibroblasts were then implanted intraperitoneally into mice immunized with bovine type II collagen. The effect of IFNbeta on paw swelling, anticollagen antibody levels, IgG1/IgG2a isotype profiles, arthritis score, histologic joint damage, and cytokine secretion from lymph node cells and from bone marrow-derived macrophages was assessed. RESULTS: A single injection of IFNbeta-secreting fibroblasts was sufficient to prevent arthritis or to ameliorate existing disease. Thus, IFNbeta reduced the clinical score and paw swelling irrespective of whether the injection was **administered** before or after disease onset in treated mice, compared with that in the untreated control group ($P < 0.05$). Histologic findings in the IFNbeta-treated mice were markedly less severe than in the control group ($P < 0.001$). This effect was accompanied by a decrease in total anticollagen IgG levels, a decrease in anticollagen IgG2a, and an increase in IgG1. In vitro, supernatants from these engineered fibroblasts inhibited collagen-induced interferon-gamma secretion from lymph node cells, and reduced the levels of tumor necrosis factor alpha and **interleukin-12** produced by lipopolysaccharide/IFNgamma-treated bone marrow-derived macrophages. This effect was specific, since it was reversed with anti-IFNbeta polyclonal antibodies. CONCLUSION: These results indicate that IFNbeta, which is currently used as a treatment for relapsing, remitting multiple sclerosis, is a potent immunomodulatory and antiinflammatory cytokine in CIA and should be considered for the **treatment** of **rheumatoid arthritis**.

L12 ANSWER 12 OF 16 MEDLINE
ACCESSION NUMBER: 1998451118 MEDLINE
DOCUMENT NUMBER: 98451118
TITLE: Circulating levels of interleukin 10 and other cytokines in **rheumatoid arthritis** **treated** with cyclosporin A or combination therapy.
AUTHOR: Ferraccioli G; Falleti E; De Vita S; Di Poi E; Damato R; Casatta L; Salaffi F
CORPORATE SOURCE: Department of Internal Medicine and Clinical Pathology, School of Medicine of Udine, Italy.. gianfranco.ferraccioli@dpmsc.uniud.it
SOURCE: JOURNAL OF RHEUMATOLOGY, (1998 Oct) 25 (10) 1874-9. Journal code: JWX. ISSN: 0315-162X.
PUB. COUNTRY: Canada
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199903
ENTRY WEEK: 19990301
AB OBJECTIVE: To assess longitudinally over a 12 month period circulating serum levels of interleukin 10 (IL-10) and cytokines IL-3, IL-4, IL-6, and **IL-12** in a cohort of patients with early onset **rheumatoid arthritis** (**RA**) **treated** with either cyclosporin A (CyA) or with combination therapy of CyA plus hydroxychloroquine as disease modifying antirheumatic drugs. METHODS: We studied 8 patients receiving CyA and 12 patients receiving CyA plus hydroxychloroquine. IL-3, IL-4, IL-6, IL-10, and **IL-12** were determined by ELISA at entry, after 2 weeks, after one month, after 6 months, and after 12 months. Rheumatoid factor levels and the possible appearance of monoclonal gammopathies over time were studied by immunofixation and immunoblotting techniques. RESULTS: The pooled data show that at entry only the median baseline levels of IL-10 (3.9 vs 1.6 pg/ml; $p < 0.01$) and IL-6 (16.9 vs 1.4 pg/ml, $p < 0.001$) were higher in patients than in controls. IL-4 was not detectable. Some patients at entry (those with the longest disease duration) had detectable levels of IL-3. Only levels of IL-10 decreased significantly between entry and final values, in monotherapy and combination therapy as well. A single transient monoclonal band was observed after 6 months of treatment, which disappeared afterwards. No difference was seen in any of the cytokines between the CyA and the CyA plus hydroxychloroquine treated patients. CONCLUSION: During treatment with either CyA or CyA plus hydroxychloroquine, IL-10 levels decreased significantly. No additive effect of the 2 drugs was detected.

L12 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:21612 BIOSIS
DOCUMENT NUMBER: PREV199900021612
TITLE: In vitro differentiation of peripheral blood T cells towards a type 2 phenotype is impaired in rheumatoid arthritis (RA.
AUTHOR(S): Asselin, S.; Conjeaud, H.; Fradelizi, D.; Breban, M. (1)
CORPORATE SOURCE: (1) Inst. Rheumatol., Hop. Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris France
SOURCE: Clinical and Experimental Immunology, (Nov., 1998) Vol. 114, No. 2, pp. 284-292.
ISSN: 0009-9104.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have examined the capacity of peripheral blood T cells from RA patients to be polarized in vitro towards a type 1 (T1) or a type 2 (T2) phenotype. Peripheral blood T cells from RA patients and from healthy donors were primed by 1 week of culture with soluble OKT3 in the presence of polarizing cytokines. The recovered T cells were

restimulated and their cytokine secretion profile determined. Priming of T cells from RA patients in the presence of recombinant (r)IL-2 plus rIL-12 induced a shift towards a T1 pattern, characterized by increased production of interferon-gamma, that was more pronounced than in the case of healthy donors. Conversely, priming of T cells from RA patients in the presence of IL-4 failed to induce a shift towards a T2 profile after 1 week, whereas it induced T cells from healthy donors to acquire such a profile characterized by heightened production of IL-4, IL-5 and IL-13. However, a T2 polarization profile emerged in T cells from RA patients that were primed in the presence of rIL-4 and subsequently maintained in culture in rIL-2 alone for 1 or 2 additional weeks. We conclude that in vitro differentiation of peripheral T cells towards a type 2 phenotype is impaired in RA. Nevertheless, conditions required to drive peripheral T cells towards a type 2 phenotype were established. **Administration** of autologous polyclonal T cells expressing a type 2 cytokine secretion profile is proposed as a **therapeutic** strategy in **RA**.

L12 ANSWER 14 OF 16 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998209799 MEDLINE
DOCUMENT NUMBER: 98209799
TITLE: Suppression of TNF-alpha expression, inhibition of Th1 activity, and amelioration of collagen-induced arthritis by rolipram.
AUTHOR: Ross S E; Williams R O; Mason L J; Mauri C; Marinova-Mutafchieva L; Malfait A M; Maini R N; Feldmann M
CORPORATE SOURCE: Kennedy Institute of Rheumatology, London, United Kingdom.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Dec 15) 159 (12) 6253-9. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199806
AB Rolipram is a type IV phosphodiesterase inhibitor that suppresses inflammation and TNF-alpha production. As anti-TNF-alpha **therapy** is effective in **rheumatoid arthritis**, we investigated the effect of rolipram on collagen-induced arthritis (CIA), a murine model of rheumatoid arthritis. Rolipram was **administered** after the onset of clinical arthritis at doses of 0.5, 3, 5, or 10 mg/kg twice daily, with a dose-dependent therapeutic effect on clinical severity and joint erosion. Immunohistochemical analysis of joints of rolipram-treated mice revealed 67% reduction in TNF-alpha-expressing cells compared with control arthritic mice. In vitro studies using

bone marrow-derived macrophages confirmed that rolipram directly suppressed TNF-alpha and **IL-12** production following stimulation with IFN-gamma and LPS. The effect of rolipram on T cell activity was studied by measuring Th1/Th2 cytokine production by collagen-stimulated draining lymph node cells from arthritic mice treated in vivo with rolipram. Rolipram reduced IFN-gamma production and increased IL-10, indicating that rolipram down-regulated the ongoing Th1 response to type II collagen. Finally, the effect on CIA of combination therapy was studied using rolipram plus either anti-TNF-alpha or anti-CD4 mAbs. Rolipram plus anti-TNF-alpha was not therapeutically additive, whereas rolipram plus anti-CD4 mAb was clearly additive. This result indicates that the therapeutic effects of rolipram overlap with TNF-alpha blockade, but are complementary to anti-CD4 treatment. It is therefore proposed that a major mechanism of action of rolipram in CIA is suppression of TNF-alpha activity. These findings suggest that type IV phosphodiesterase inhibitors may be effective in pathologic conditions, such as RA, with overexpression of TNF-alpha.

L12 ANSWER 15 OF 16 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1995-076349 [11] WPIDS
CROSS REFERENCE: 2000-302667 [25]
DOC. NO. NON-CPI: N1995-060614
DOC. NO. CPI: C1995-033954
TITLE: DNA encoding a low affinity **interleukin-12** receptor - used to bind or scavenge **IL-12** to cause immune suppression, e.g. to suppress graft-vs-host reaction, allograft rejection or inflammation, and to treat autoimmune conditions.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): CHIZZONITE, R A; CHUA, A O; GUBLER, U A; TRUITT, T P; ON CHUA, A
PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE INC
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 638644	A1	19950215	(199511)*	EN	61
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
AU 9467505	A	19950127	(199512)		
CA 2128151	A	19950120	(199516)		
ZA 9405154	A	19950329	(199519)		96
JP 07194383	A	19950801	(199539)		40
NZ 264003	A	19951221	(199606)		
US 5536657	A	19960716	(199634)		47
AU 676325	B	19970306	(199718)		

Searcher : Shears 308-4994

US 5831007 A 19981103 (199851)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 638644	A1		EP 1994-110657	19940708
AU 9467505	A		AU 1994-67505	19940715
CA 2128151	A		CA 1994-2128151	19940715
ZA 9405154	A		ZA 1994-5154	19940714
JP 07194383	A		JP 1994-166950	19940719
NZ 264003	A		NZ 1994-264003	19940714
US 5536657	A	CIP of	US 1993-94713	19930719
			US 1994-248532	19940531
AU 676325	B		AU 1994-67505	19940715
US 5831007	A	CIP of	US 1993-94713	19930719
		Div ex	US 1994-248532	19940531
			US 1995-419652	19950411

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 676325	B	Previous Publ.	AU 9467505
US 5831007	A	Div ex	US 5536657

PRIORITY APPLN. INFO: US 1994-248532 19940531; US 1993-94649 19930719; US 1993-94713 19930719; US 1995-419652 19950411

AN 1995-076349 [11] WPIDS

CR 2000-302667 [25]

AB EP 638644 A UPAB: 20000531

DNA encoding a low affinity **interleukin-12** (**IL-12**) receptor (IL-12R) or deriv. is claimed.

Also claimed are: (1) a vector comprising the DNA; (2) a host cell transformed with the vector; (3) a low affinity IL-12R or deriv.; (4) an immunoglobulin (Ig) which binds selectively to IL-12R; (5) a compsn. comprising human cells activated to express IL-12R bound with the labelled Ig; (6) method for detecting an IL-12R by isolating cells from the subject that express IL-12R, contacting the cells with a detectable Ig specific for IL-12R, incubating the cells and detecting cell binding to the Ig; and (7) detecting soluble IL-12R by capturing the receptor with an Ig, and carrying out a binding assay with labelled **IL-12**.

USE - IL-12R is used to bind or scavenge **IL-12**. It is useful to treat diseases caused by an immune response to alloantigen, and in the treatment of autoimmune dysfunction. IL-12R can be **administered** to cause immune suppression in a human, e.g. to suppress graft-vs-host reaction,

allograft rejection, lymphoproliferation and inflammation. It can also be used to **treat** autoimmune conditions, e.g. **rheumatoid arthritis**, diabetes and multiple sclerosis, IL-12R can also be used in diagnostic assays for **IL-12** or IL-12R, and for raising antibodies useful in diagnosis or therapy. The Ig is useful for neutralising and/or inhibiting **IL-12** bioactivity. It also can be used to determine an immune system abnormality in a subject, by determn. of the number of T, NK or B cells in a sample by determining the percentages of cells in a sample with IL-12R, and comparing these percentages with those from a normal subject.
Dwg.0/19

ABEQ US 5536657 A UPAB: 19960829
A substantially pure, homogenous and isolated DNA encoding a human low affinity **Interleukin-12** receptor protein comprising either a 660 or 662 amino acid sequence given in the specification which binds specifically to **interleukin-12**.
Dwg.0/19

L12 ANSWER 16 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94060121 EMBASE
DOCUMENT NUMBER: 1994060121
TITLE: [Pediatric applications of cytokines].
EINSATZ VON ZYTOKINEN IN DER PADIATRIE.
AUTHOR: Gadner H.
CORPORATE SOURCE: St. Anna Kinderspital, Kinderspitalgasse 6,A-1090 Wien, Germany
SOURCE: Klinische Padiatrie, (1994) 206/1 (2-11).
ISSN: 0300-8630 CODEN: KLPDB2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: German; English
AB Cytokines are decisive for the regulation of the immune system as well as the renewal and maturation of the haematopoetic cells. The most important groups of substances, several of which are already produced by gentechnology, are the interferons, the interleukins and the haematopoetic growth factors. The main indications for the application of .alpha.-(less often .beta.-)Interferon in children are the juvenile larynxpapillomatosis, chronic hepatitis B, viral encephalitis, and also chronic myeloic leukemia, extended haemangiomas, recurrent Langerhans cell histiocytosis and nasopharynx-carcinomas. .gamma.-Interferon is **administered** successfully for chronic granulomatons disease and has recorded

positive effects in **therapy** resistent **rheumatoid arthritis**, in kidney cell carcinoma and in osteopetrosis. G-CSF, GM-CSF and Interleukin 3 are the most effective haematopoetic growth factors currently in use. Through G-CSF congenital agranulocytosis (Kostmann syndrome) has become a treatable disease. Other proven applications are in the reduction of aplastic phases after chemotherapy and in critical situations of primary bone marrow failure as well as myelodysplastic syndromes, for prevention of transplant rejections after bone marrow transplantation and for mobilisation of stem cells into peripheral blood before apharesis. Erythropoietin is established in the treatment of chronic renal anaemia and is currently used in the treatment of anaemia in preterm infants. Finally, Interleukin 2 is also used for adoptive immunotherapy in children with minimal residual tumors. The future will show us, whether the spectrum of indications will expand and whether a definit benefit for sick children will result from a wider application of these substances. As long as the cost/benefit ratio for certain indications is not clear, the use of these drugs should be tested in prospective studies.

FILE 'CAPLUS' ENTERED AT 12:10:54 ON 06 MAR 2001
L13 117 S L4(S)ANTAGONIST?
L14 9 S L13 AND (RA OR RHEUMAT? ARTHRIT?)
L15 7 S L14 NOT L7

L15 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:688272 CAPLUS
DOCUMENT NUMBER: 133:280563
TITLE: Human antibodies that bind human IL-12 and methods for producing
INVENTOR(S): Salfeld, Jochen G.; Roguska, Michael; Paskind, Michael; Banerjee, Subhashis; Tracey, Daniel E.; White, Michael; Kaymakcalan, Zehra; Labkovsky, Boris; Sakorafas, Paul; Friedrich, Stuart; Myles, Angela; Veldman, Geertruida M.; Venturini, Amy; Warne, Nicholas W.; Widom, Angela; Elvin, John G.; Duncan, Alexander R.; Derbyshire, Elaine J.; Carmen, Sara; Smith, Stephen; Holtet, Thor Las; Du, Fou Sarah L.
PATENT ASSIGNEE(S): Basf A.-G., Germany; Genetics Institute Inc.; et al.
SOURCE: PCT Int. Appl., 377 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000056772	A1	20000928	WO 2000-US7946	20000324

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-126603 19990325

AB Human antibodies, preferably recombinant human antibodies, that specifically bind to human interleukin-12 (hIL-12) are disclosed. Preferred antibodies have high affinity for hIL-12 and neutralize hIL-12 activity in vitro and in vivo . An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. The antibodies, or antibody portions, of the invention are useful for detecting hIL-12 and for inhibiting hIL-12 activity, e.g., in a human subject suffering from a disorder in which hIL-12 activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human antibodies of the invention, and methods of synthesizing the recombinant human antibodies, are also encompassed by the invention.

REFERENCE COUNT: 7

REFERENCE(S):
(2) Carter, R; HYBRIDOMA 1997, V16(4), P363 CAPLUS
(3) Genentech Inc; WO 9404679 A 1994 CAPLUS
(4) Genetics Inst; WO 9524918 A 1995 CAPLUS
(5) Irving, R; IMMUNOTECHNOLOGY 1996, V2(2), P127 CAPLUS
(6) Pini, A; JOURNAL OF IMMUNOLOGICAL METHODS 1997, V206(1-2), P171 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:2517 CAPLUS

DOCUMENT NUMBER: 132:106828

TITLE: Ligand-activation of the adenosine A2a receptors inhibits IL-12 production by human monocytes

AUTHOR(S): Link, Amrey A.; Kino, Tomoshige; Worth, James A.; McGuire, Jennifer L.; Crane, Marianna L.; Chrousos, George P.; Wilder, Ronald L.; Elenkov, Ilia J.

CORPORATE SOURCE: Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: J. Immunol. (2000), 164(1), 436-442

Searcher : Shears 308-4994

CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adenosine (ADO) exerts potent anti-inflammatory and immunosuppressive effects. In this paper we address the possibility that these effects are partly mediated by inhibition of the secretion of IL-12, a proinflammatory cytokine and a major inducer of Th1 responses. We demonstrate that 5'-N-ethylcarboxamidoadenosine (NECA), a nonspecific ADO analog, and 2-p-(2-carbonylethyl)phenylethylamino-5'-N-ethylcarboxamidoadenosine (CGS-21680), a specific A2a receptor agonist, dose-dependently inhibited, in whole blood ex vivo and monocyte cultures, the prodn. of human IL-12 induced by LPS and Staphylococcus aureus Cowan strain 1. However, the A1 receptor agonist 2-chloro-N6-cyclopentyladenosine and the A3 receptor agonists N6-benzyl-NECA and 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl-.beta.-D-ribofuranuronamide expressed only weak inhibitory effects. On the other hand, NECA and CGS-21680 dose-dependently potentiated the prodn. of IL-10. The differential effect of these drugs on monocyte IL-12 and IL-10 prodn. implies that these effects are mediated by A2a receptor signaling rather than by intracellular toxicity of ADO analog's metabolites. Moreover, CGS-21680 inhibited IL-12 prodn. independently of endogenous IL-10 induction, because anti-IL-10 Abs failed to prevent its effect. The selective A2a **antagonist** 8-(3-chlorostyryl) caffeine prevented the inhibitory effect of CGS-21680 on **IL-12** prodn. The phosphodiesterase inhibitor Ro 20-1724 dose-dependently potentiated the inhibitory effect of CGS-21680 and, furthermore, Rp-cAMPS, a protein kinase A inhibitor, reversed the inhibitory effect of CGS-21680, implicating a cAMP/protein kinase A pathway in its action. Thus, ligand activation of A2a receptors simultaneously inhibits IL-12 and stimulates IL-10 prodn. by human monocytes. Through this mechanism, ADO released in excess during inflammatory and ischemic conditions, or tissue injury, may contribute to selective suppression of Th1 responses and cellular immunity.

REFERENCE COUNT: 36
REFERENCE(S):
(1) Bouma, M; J Immunol 1994, V153, P4159 CAPLUS
(2) Burnstock, G; Neuropharmacology 1997, V36, P1127 CAPLUS
(3) Cain, B; J Surg Res 1998, V76, P117 CAPLUS
(5) Cronstein, B; J Clin Invest 1993, V92, P2675 CAPLUS
(6) Cronstein, B; J Exp Med 1983, V158, P1160 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:487326 CAPLUS
Searcher : Shears 308-4994

DOCUMENT NUMBER: 131:129052
TITLE: Antibodies against human IL-12
INVENTOR(S): Gately, Maurcie Kent; Presky, David Howard
PATENT ASSIGNEE(S): F.Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9937682	A2	19990729	WO 1999-EP202	19990115
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9925177	A1	19990115	AU 1999-25177	19990115
BR 9907743	A	20001017	BR 1999-7743	19990115
EP 1049717	A2	20001108	EP 1999-904780	19990115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1998-72333	19980123
			WO 1999-EP202	19990115

AB The present invention relates to p75 heterodimer specific anti-human IL-12 antibodies that are characterized by a higher potency and greater efficacy in neutralizing human IL-12 bioactivity than known heterodimer specific IL-12 monoclonal antibodies. The heterodimer specific antibodies recognize one or more epitopes of the human IL-12 p75 heterodimer, but do not bind to the p40 subunit alone. The heterodimer specific **IL-12** antibodies neutralize rhesus monkey **IL-12** bioactivity with a potency similar to their potency for neutralizing human **IL-12** bioactivity making them useful **IL-12 antagonists**. The monoclonal antibodies are therefore useful for diseases assocd. with aberrant Th1-type helper cell activity, e.g. multiple sclerosis, **rheumatoid arthritis**, autoimmune diabetes mellitus, Crohn's disease and ulcerative colitis.

L15 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:69433 CAPLUS
DOCUMENT NUMBER: 130:280409

TITLE: Redirecting Th1 and Th2 responses in autoimmune disease
AUTHOR(S): Pearson, C. I.; McDevitt, H. O.
CORPORATE SOURCE: Department of Microbiology and Immunology, Stanford University Medical Center, Stanford, CA, 94305, USA
SOURCE: Curr. Top. Microbiol. Immunol. (1999), 238(Redirection of Th1 and Th2 Responses), 79-122
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with approx. 240 refs. Discussed are: multiple sclerosis and exptl. autoimmune encephalomyelitis as Th1-mediated diseases; insulin-dependent diabetes mellitus as a Th1-mediated disease; **rheumatoid arthritis** and collagen-induced arthritis as Th1-mediated diseases; genetic influences on Th1/Th2 development in autoimmunity; therapies of autoimmune disease; exogenous cytokines and antibodies to cytokines as therapy; **interleukin-12 antagonists** as therapy; antigen-specific therapies of autoimmunity; specific antigen therapy reduces exptl. autoimmune encephalomyelitis; myelin basic protein-specific TCR receptor transgenic mice; apoptosis and Th differentiation correlate with peptide affinity for MHC; altered peptide ligands can induce Th2 responses as therapy for exptl. autoimmune encephalomyelitis; specific antigen therapy in insulin-dependent diabetes deviates response from Th1 to Th2; oral tolerance as specific antigen therapy; costimulatory mols. as targets for therapy; expression of class II MHC mols. protects from diabetes; and neonatal tolerance.

REFERENCE COUNT: 215
REFERENCE(S):
(2) Al-Sabbagh, A; J Neurosci Res 1996, V45, P424 CAPLUS
(3) Alam, S; Nature 1996, V381, P616 CAPLUS
(5) Baker, D; J Immunol 1995, V155, P4046 CAPLUS
(6) Balashov, K; Proc Natl Acad Sci USA 1997, V94, P599 CAPLUS
(7) Baron, J; J Exp Med 1993, V177, P57 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:493693 CAPLUS
DOCUMENT NUMBER: 129:121651
TITLE: Compounds, compositions and methods for the endocytic presentation of immunosuppressive factors
INVENTOR(S): Zaghouani, Habib
PATENT ASSIGNEE(S): Alliance Pharmaceutical Corp., USA; Zaghouani,

Habib
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830706	A1	19980716	WO 1998-US520	19980107
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9858214	A1	19980803	AU 1998-58214	19980107
EP 1012308	A1	20000628	EP 1998-901773	19980107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1997-779767	19970107
			WO 1998-US520	19980107

AB Immunomodulating agents comprising at least one Fc receptor ligand and at least one immunosuppressive factor are provided as are methods for their manuf. and use. The immunomodulating agents may be in the form of polypeptides or chimeric antibodies and preferably incorporate an immunosuppressive factor comprising a T cell receptor antagonist or agonist. The compds. and compns. of the invention may be used to selectively suppress the immune system to treat symptoms assocd. with immune disorders such as allergies, transplanted tissue rejection and autoimmune disorders including lupus, **rheumatoid arthritis** and multiple sclerosis.

L15 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:351787 CAPLUS
DOCUMENT NUMBER: 129:40158
TITLE: Suppression of TNF.alpha. and IL-12 in therapy
INVENTOR(S): Feldmann, Marc; Malfait, Anne-Marie Aline Michel; Butler, Debra Maree; Brennan, Fionula Mary; Maini, Ravinder Nath
PATENT ASSIGNEE(S): Kennedy Institute of Rheumatology, UK; Feldmann, Marc; Malfait, Anne-Marie Aline Michel; Butler, Debra Maree; Brennan, Fionula Mary; Maini, Ravinder Nath
SOURCE: PCT Int. Appl., 66 pp.
Searcher : Shears 308-4994

TITLE: Redirecting Th1 and Th2 responses in autoimmune disease
AUTHOR(S): Pearson, C. I.; McDevitt, H. O.
CORPORATE SOURCE: Department of Microbiology and Immunology, Stanford University Medical Center, Stanford, CA, 94305, USA
SOURCE: Curr. Top. Microbiol. Immunol. (1999), 238(Redirection of Th1 and Th2 Responses), 79-122
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with approx. 240 refs. Discussed are: multiple sclerosis and exptl. autoimmune encephalomyelitis as Th1-mediated diseases; insulin-dependent diabetes mellitus as a Th1-mediated disease; **rheumatoid arthritis** and collagen-induced arthritis as Th1-mediated diseases; genetic influences on Th1/Th2 development in autoimmunity; therapies of autoimmune disease; exogenous cytokines and antibodies to cytokines as therapy; **interleukin-12 antagonists** as therapy; antigen-specific therapies of autoimmunity; specific antigen therapy reduces exptl. autoimmune encephalomyelitis; myelin basic protein-specific TCR receptor transgenic mice; apoptosis and Th differentiation correlate with peptide affinity for MHC; altered peptide ligands can induce Th2 responses as therapy for exptl. autoimmune encephalomyelitis; specific antigen therapy in insulin-dependent diabetes deviates response from Th1 to Th2; oral tolerance as specific antigen therapy; costimulatory mols. as targets for therapy; expression of class II MHC mols. protects from diabetes; and neonatal tolerance.

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(2) Al-Sabbagh, A; J Neurosci Res 1996, V45, P424 CAPLUS
(3) Alam, S; Nature 1996, V381, P616 CAPLUS
(5) Baker, D; J Immunol 1995, V155, P4046 CAPLUS
(6) Balashov, K; Proc Natl Acad Sci USA 1997, V94, P599 CAPLUS
(7) Baron, J; J Exp Med 1993, V177, P57 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:493693 CAPLUS
DOCUMENT NUMBER: 129:121651
TITLE: Compounds, compositions and methods for the endocytic presentation of immunosuppressive factors
INVENTOR(S): Zaghouani, Habib
PATENT ASSIGNEE(S): Alliance Pharmaceutical Corp., USA; Zaghouani,

Habib
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830706	A1	19980716	WO 1998-US520	19980107
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9858214	A1	19980803	AU 1998-58214	19980107
EP 1012308	A1	20000628	EP 1998-901773	19980107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1997-779767	19970107
			WO 1998-US520	19980107

AB Immunomodulating agents comprising at least one Fc receptor ligand and at least one immunosuppressive factor are provided as are methods for their manuf. and use. The immunomodulating agents may be in the form of polypeptides or chimeric antibodies and preferably incorporate an immunosuppressive factor comprising a T cell receptor antagonist or agonist. The compds. and compns. of the invention may be used to selectively suppress the immune system to treat symptoms assocd. with immune disorders such as allergies, transplanted tissue rejection and autoimmune disorders including lupus, **rheumatoid arthritis** and multiple sclerosis.

L15 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:351787 CAPLUS
DOCUMENT NUMBER: 129:40158
TITLE: Suppression of TNF.alpha. and IL-12 in therapy
INVENTOR(S): Feldmann, Marc; Malfait, Anne-Marie Aline Michel; Butler, Debra Maree; Brennan, Fionula Mary; Maini, Ravinder Nath
PATENT ASSIGNEE(S): Kennedy Institute of Rheumatology, UK; Feldmann, Marc; Malfait, Anne-Marie Aline Michel; Butler, Debra Maree; Brennan, Fionula Mary; Maini, Ravinder Nath
SOURCE: PCT Int. Appl., 66 pp.
Searcher : Shears 308-4994

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822137	A1	19980528	WO 1997-GB3151	19971117
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9749599	A1	19980610	AU 1997-49599	19971117
EP 936923	A1	19990825	EP 1997-912367	19971117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1996-749979	19961115
			WO 1997-GB3151	19971117

AB Methods for treating and/or preventing a TNF.alpha.-mediated disease in an individual are disclosed. Also disclosed are compns. comprising a TNF **antagonist** and an **IL-12 antagonist**. The TNF.alpha. **antagonist** is an antibody or a TNF receptor/IgG fusion protein or thalidomide, and the **IL-12 antagonist** is an antibody or phosphodiesterase inhibitor, e.g. pentoxifylline or rolipram. TNF.alpha.-mediated diseases include **rheumatoid arthritis**, Crohn's disease, and acute and chronic immune diseases assocd. with transplantation.

L15 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:565025 CAPLUS
DOCUMENT NUMBER: 125:219235
TITLE: Opposite effects of interleukin-13 and interleukin-12 on the release of inflammatory cytokines, cytokine inhibitors and prostaglandin E from synovial fibroblasts and blood mononuclear cells
AUTHOR(S): Seitz, Michael; Loetscher, Pius; Dewald, Beatrice; Towbin, Harry; Baggiolini, Marco
CORPORATE SOURCE: Div. Rheumatology, Univ. Hospital, Bern, Switz.
SOURCE: Eur. J. Immunol. (1996), 26(9), 2198-2202
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal

LANGUAGE: English

AB We examd. the effects of interleukin-12 (IL-12) and interleukin-13 (IL-13) on cytokine, cytokine inhibitor and prostaglandin E (PGE) release from synovial fibroblasts and blood mononuclear cells (MNC). In resting synovial fibroblasts, we found that IL-13 is an inhibitor of IL-8 and PGE release. A significant decrease of PGE synthesis caused by IL-13 was also obsd. in tumor necrosis factor (TNF)-.alpha.-stimulated synovial fibroblasts, whereas IL-12 had no regulatory effects on these cells. In resting and cytokine-stimulated MNC, IL-13 markedly inhibited IL-1.beta., IL-8 and monocyte chemoattractant protein-1 (MCP-1) release and potently stimulated interleukin-1 receptor antagonist (IL-1ra) synthesis. In contrast, IL-12 stimulated the prodn. of IL-1.beta. and MCP-1 in TNF-.alpha.-stimulated MNC and inhibited IL-1ra synthesis in cytokine-stimulated cells. These findings identify novel biol. actions of IL-12 and IL-13 on connective tissue and on blood mononuclear cells which indicate their regulatory function an enhancer and suppressor of inflammatory processes, resp.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:12:04 ON 06 MAR 2001)

L16 17 S L14
L17 17 S L16 NOT L11
L18 15 DUP REM L17 (2 DUPLICATES REMOVED)

L18 ANSWER 1 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2001014007 EMBASE
TITLE: Reduced incidence and severity of collagen-induced arthritis in mice lacking IL-18.
AUTHOR: Wei X.-Q.; Leung B.P.; Arthur H.M.L.; McInnes I.B.; Liew F.Y.
CORPORATE SOURCE: Dr. F.Y. Liew, Dept. of Immunology/Bacteriology, University of Glasgow, Glasgow G11 6NT, United Kingdom. F.Y.Liew@clinmed.gla.ac.uk
SOURCE: Journal of Immunology, (1 Jan 2001) 166/1 (517-521). Refs: 31
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have recently reported the presence and a potential proinflammatory role of IL-18 in the synovium of patients with **rheumatoid arthritis**. To obtain direct evidence that IL-18 plays an influential role in articular inflammation, we investigated the development of collagen-induced arthritis in a strain of mice lacking IL-18 (IL-18(-/-)) of DBA/1 background.

IL-18(-/-) mice developed markedly reduced incidence of arthritis compared with heterozygous or wild-type mice. Of the IL-18(-/-) mice that developed arthritis, the severity of the disease was significantly reduced compared with the intact mice. This was accompanied by reduced articular inflammation and destruction evident on histology. IL-18(-/-) mice also had significantly reduced Ag-specific proliferation and proinflammatory cytokine (IFN-.gamma., TNF-.alpha., IL-6, and **IL-12**) production by spleen and lymph node cells in response to bovine type II collagen (CII) in vitro compared with wild-type mice, paralleled in vivo by a significant reduction in serum anti-CII IgG2a Ab level. Treatment with rIL-18 completely reversed the disease of the IL-18(-/-) mice to that of the wild-type mice. These data directly demonstrate a pivotal role of IL-18 in the development of inflammatory arthritis and suggest that **antagonists** to IL-18 may have therapeutic potential in rheumatic diseases.

L18 ANSWER 2 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-049688 [06] WPIDS
DOC. NO. CPI: C2001-013577
TITLE: New agonists or **antagonists** of haemopoietic growth factors for treating myeloid and lymphocyte leukemias, tumors and acute and chronic inflammation such as asthma, **rheumatoid arthritis** and atherosclerosis.
DERWENT CLASS: B04 D16
INVENTOR(S): BAGLEY, C; D'ANDREA, R; VADAS, M A
PATENT ASSIGNEE(S): (MEDV-N) MEDVET SCI PTY LTD
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000066632	A1	20001109	(200106)*	EN	35

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000040931 A 20001117 (200111)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000066632	A1	WO 2000-AU394	20000501

Searcher : Shears 308-4994

AU 2000040931 A AU 2000-40931 20000501

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000040931 A	Based on	WO 200066632

PRIORITY APPLN. INFO: AU 1999-53 19990429
AN 2001-049688 [06] WPIDS
AB WO 200066632 A UPAB: 20010126
NOVELTY - An agonist (I) or **antagonist** (II) of an haemopoietic growth factor which is capable of binding a region of the CRD3 of h beta c or analogous domain of a corresponding haemopoietic growth factor receptor to impact an interaction between CRD3 and CRD4 or analogous domains to effect an agonist or **antagonist** property, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(a) a method for isolating (I) or (II);

(b) a pharmaceutical use of (I) or (II).

ACTIVITY - Cytostatic; antiasthmatic; antirheumatic; antiarthritic; antiarteriosclerotic. No biological data is given.

MECHANISM OF ACTION - Haemopoietic growth factor agonist/ **antagonist**.

USE - (I) or (II) is used for treating conditions currently treated by granulocyte macrophage colony stimulating factor (GM-CSF), interleukin (IL)-3, IL-5 and other members of the family of haemopoietic growth factors. **Antagonists** are useful e.g. for treating myeloid and lymphocyte leukemias, tumors or non-haemopoeitic origins and acute and chronic inflammation such as asthma, **rheumatoid arthritis** and atherosclerosis.

Dwg.0/7

L18 ANSWER 3 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-579362 [54] WPIDS
DOC. NO. CPI: C2000-172507
TITLE: New pyrazolo(1,5-a)pyrimidin-6-yl-1H-(pyridin- or pyrimidin)-2-one derivatives, useful for treating tyrosine kinase-dependent diseases e.g. angiogenesis, cancer, tumor growth, atherosclerosis and age related macular degeneration.
DERWENT CLASS: B02
INVENTOR(S): BILODEAU, M T; FRALEY, M E; HUNGATE, R W
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000053605	A1	20000914	(200054)*	EN	57

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000036179 A 20000928 (200067)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000053605	A1	WO 2000-US5903	20000308
AU 2000036179	A	AU 2000-36179	20000308

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000036179	A	Based on	WO 200053605

PRIORITY APPLN. INFO: US 1999-123902 19990311

AN 2000-579362 [54] WPIDS

AB WO 200053605 A UPAB: 20001027

NOVELTY - Pyrazolo(1,5-a)pyrimidin-6-yl-1H-(pyridin- or pyrimidin)-2-one derivatives (I) and their salts and stereoisomers are new.

DETAILED DESCRIPTION - Pyrazolo(1,5-a)pyrimidin-6-yl-1H-(pyridin- or pyrimidin)-2-one derivatives of formula (I) and their salts and stereoisomers are new.

X = CH or N;

R1, R3 = H, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, aryl, halo, OH or heterocyclyl where alkyl, alkenyl, alkynyl, aryl and heterocyclyl are optionally substituted by 1-3 **Ra**;

R2 = H, 1-6C alkyl, aryl, OH, NO2, NH2 or halo;

R5 = H, 1-6C alkyl, OH, O-1-6C alkyl, halo, NH2 or NO2;

R7, R8 = H, 1-10C alkyl, COR, COOR, aryl or heteroaryl where alkyl, aryl and heterocyclyl are optionally substituted by R9; or

NR7R8 = 5-10 membered optionally saturated heterocyclyl containing in addition to the N atom, 1 or 2 additional N, O or S, and the ring is optionally substituted by 1 or 2 **Ra**;

R9 = aryl or heterocyclyl (optionally substituted by 1-3 **Ra**);

R10 = H, 1-6C alkyl, NR7R8, O-1-6C alkyl, aryl or heterocyclyl, where alkyl, aryl and heterocyclyl are optionally substituted by 1-3 **Ra**;

Ra = 1-10C alkyl, halo, NO2, OR, NR7R8, CN, aryl or heterocyclyl;

R = H or 1-6C alkyl.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising (I) and a second compound selected from: (i) an estrogen receptor modulator; (ii) an androgen receptor modulator; (iii) retinoid receptor modulator; (iv) a cytotoxic agent; (v) an antiproliferative agent; (vi) a prenyl-protein transferase inhibitor; (vii) an HMG-CoA reductase inhibitor; (viii) an HIV protease inhibitor; (ix) a reverse transcriptase inhibitor; and (x) another angiogenesis inhibitor;

(2) treatment or prevention of cancer comprising administering: (a) (I) in combination with radiation therapy and/or with second compound as in (1); (b) (I) in combination with paclitaxel or trastuzumab; or (c) (I) in combination with GPIIb/IIIa **antagonist**.

MECHANISM OF ACTION - Tyrosine kinase inhibitor.

In a VEGF receptor kinase assay, compounds (I) inhibited VEGF-stimulated mitogenesis of human endothelial cells in culture with IC50 values of 0.01-5.0 micro M. The compounds also showed selectivity over related tyrosine kinases (e.g. FGFR1 and the Src family).

USE - For treating or preventing tyrosine kinase dependent diseases and conditions, especially cancer in a mammal, particularly brain, genitourinary tract, lymphatic system, stomach, larynx and lung cancers; histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, gioblastomas and breast carcinoma; for treating and preventing diseases in which angiogenesis is implicated, especially ocular disease; for treating and preventing retinal vascularization, diabetic retinopathy, age related macular degeneration, inflammatory diseases especially **rheumatoid arthritis**, psoriasis, contact dermatitis and delayed hypersensitivity reactions; bone associated pathologies especially osteosarcoma, osteoarthritis and rickets (all claimed).

Dwg.0/0

L18 ANSWER 4 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-465950 [40] WPIDS

DOC. NO. CPI: C2000-140345

TITLE: Identification of compounds that modulate cytokine release by alphaE-beta7-expressing cells and that can be used as **antagonists** and agonists of Th2 cytokine release for treating e.g. allergic and autoimmune diseases.

DERWENT CLASS: B04 C03 D16 J04

INVENTOR(S): ARYA, A; BRENNER, M B; CARR, M W; PARKER, C M

PATENT ASSIGNEE(S): (BGHM) BRIGHAM & WOMENS HOSPITAL INC

COUNTRY COUNT: 90

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040604	A2	20000713	(200040)*	EN	79
AU 2000023904	A	20000724	(200052)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040604	A2	WO 1999-US30992	19991228
AU 2000023904	A	AU 2000-23904	19991228

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000023904	A	Based on	WO 200040604

PRIORITY APPLN. INFO: US 1999-115055 19990108

AN 2000-465950 [40] WPIDS

AB WO 200040604 A UPAB: 20000823

NOVELTY - Screening methods for identifying compounds that modulate cytokine release by alpha E beta 7-expressing cells, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a screening method for identifying compounds that modulate cytokine release by alpha E beta 7-expressing cells comprising:

(a) performing a first cytokine release assay to measure cytokine release by a stimulated alpha E beta 7-expressing cell;

(b) performing a second cytokine release assay to measure cytokine release by an alpha E beta 7-expressing cell in the presence of one or more test compounds; and

(c) comparing the first and second cytokine release assay results to determine whether the test compound modulates cytokine release by the alpha E beta 7-expressing cell;

(2) a screening method for selecting an alpha E **antagonist** that blocks a Th2 cytokine response by a stimulated alpha E beta 7-expressing cell comprising:

(a) contacting a alpha E beta 7-expressing cell with a test compound to allow the test compound to bind to the alpha E beta 7 integrin expressed on the cell's surface;

(b) determining the amount and/or identity of one or more

cytokines released by the alpha E beta 7-expressing cell; and

(c) selecting as an **antagonist** a test compound which decreases the release of a Th2 cytokine by the alpha E beta 7-expressing cell or which increases the amount of a Th1 cytokine or of **interleukin-12 (IL-12)** compared to the release of these cytokines by cells not contacted with the test compound; and

(3) a screening method for selecting an alpha E agonist for activating a Th2 cytokine response by a stimulated alpha E beta 7-expressing cell comprising:

(a) contacting a stimulated alpha E beta 7-expressing cell with a test compound to allow the test compound to bind to an alpha E beta 7 integrin expressed on the cell's surface;

(b) determining the amount and/or identity of one or more cytokines released by the alpha E beta 7-expressing cell; and

(c) selecting as an agonist a test compound which increases the release of a Th2 cytokine by the alpha E beta 7-expressing cell or which decreases the amount of a Th1 cytokine or of **interleukin-12 (IL-12)** compared to the release of these cytokines by cells not contacted with the test compound.

ACTIVITY - Antidiabetic; antiasthmatic; antiallergic; opthalmalogical; antiinflammatory; tuberculostatic; protozoacide; antiarthritic; antirheumatic; neuroprotective; antipsoriatic.

No suitable biological data is given.

MECHANISM OF ACTION - **Antagonist** and agonist of Th2 cytokine response by alpha E beta 7-expressing cell.

USE - alpha E **antagonists** that are selected by the methods are used to treat a condition mediated by an increase in release in Th2 cytokines by an alpha E beta 7-expressing cell e.g. allergic asthma, allergic conjunctivitis, allergic rhinitis, contact hypersensitivity, or for treating a condition mediated by a decrease in release of Th1 cytokines by a alpha E beta 7-expressing cell e.g. infectious diseases such as tuberculosis or Helminth infection and also for treating an inflammatory bowel disease. alpha E agonists that are selected by the methods are used to treat a condition mediated by a decrease in release in Th2 cytokines by an alpha E beta 7-expressing cell or for treating a condition mediated by a decrease in release of Th1 cytokines by a alpha E beta 7-expressing cell e.g. inflammatory and autoimmune conditions such as **rheumatoid arthritis**, multiple sclerosis, type 1 diabetes, psoriasis or inflammatory bowel disease. (All claimed). Dwg.0/11

L18 ANSWER 5 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-205894 [18] WPIDS
DOC. NO. CPI: C2000-063611
TITLE: New bioconjugates comprising an avb3 **antagonist** and a metastatic-associated

receptor ligand, useful for treating cancer and other angiogenic diseases, or as antiviral, antifungal or antibacterial agents.

DERWENT CLASS: B04 D16
INVENTOR(S): FOK, K F; TJOENG, F S
PATENT ASSIGNEE(S): (SEAR) SEARLE & CO G D
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000009143	A1	20000224	(200018)*	EN	123

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9934498	A	20000306	(200030)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000009143	A1	WO 1999-US4296	19990407
AU 9934498	A	AU 1999-34498	19990407

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9934498	A	Based on	WO 200009143

PRIORITY APPLN. INFO: US 1998-96442 19980813
AN 2000-205894 [18] WPIDS
AB WO 200009143 A UPAB: 20000412
NOVELTY - A novel bioconjugate comprises one or more avb3 **antagonist** moieties coupled to an amide or to a metastasis-associated receptor ligand by a covalent bond or by a linear or branched linker.

ACTIVITY - Cytostatic; Osteopathic; Antirheumatic; Antiarthritic; Antidiabetic; Ophthalmological; Antiinflammatory; Antipsoriatic; Thrombolytic; Antianginal; Antiarteriosclerotic; Vasotropic; Antiviral; Antifungal; ANtibacterial.

MECHANISM OF ACTION - Avb3 integrin **antagonists**. In a solid phase avb3 binding assay ((A'-GDS-GGG GA)2 K)2 K-AGAGA-IFN-alpha (Ia) had an IC50 = 0.13nM. (A' = 3-(1,4,5,6-tetrahydro-2-pyrimidyl)amino benzoyl).

USE - The conjugates can be used for treating a human patient

with an angiogenesis-mediated disease, e.g. cancer, arthritis, or macular degeneration (claimed). They can be used for inhibiting elevated levels of tumor antigens, inhibiting the proliferation of tumor cells and inhibiting tumor growth (claimed). The tumor cells may be e.g. lung cancer, breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, gastric cancer, colon cancer, renal cancer, bladder cancer, melanoma, hepatoma, sarcoma or lymphoma (claimed). The bioconjugates can also be used for treating e.g. osteoporosis, humoral hypercalcemia of malignancy, Paget's disease, retinopathy including diabetic retinopathy, arthritis, including **rheumatoid arthritis**, periodontal disease, psoriasis, thrombosis, angina, atherosclerosis, smooth muscle cell migration and restenosis in a mammal. They are also useful as antiviral, antifungal and antibacterial agents.

ADVANTAGE - Multi-functional bioconjugates can exhibit useful properties such as having similar or greater biological activity when compared to a single factor or having improved half-life or decreased adverse side effects, or a combination of these properties.

Dwg.0/0

L18 ANSWER 6 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-561651 [47] WPIDS
CROSS REFERENCE: 1999-180042 [15]
DOC. NO. CPI: C1999-163646
TITLE: New 2-(2,6-dioxo-3-fluoropiperidin-3-yl)-isoindoline inflammatory cytokine **antagonists**, used e.g. for treating arthritis, sepsis, psoriasis or viral infection.
DERWENT CLASS: B02 C02
INVENTOR(S): CHEM, R S; MAN, H; MULLER, G W; STIRLING, D I; CHEN, R S
PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9946258	A1	19990916	(199947)*	EN	32
US 5955476	A	19990921	(199947)		
AU 9914138	A	19990927	(200006)		
NO 2000002529	A	20000630	(200045)		
FI 2000001192	A	20000714	(200051)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

CZ 2000001822 A3 20001115 (200064)
EP 1062214 A1 20001227 (200102) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
SK 2000000738 A3 20001211 (200103)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9946258	A1		WO 1998-US24453	19981117
US 5955476	A	CIP of	US 1997-976140	19971118
			US 1998-42274	19980313
AU 9914138	A		AU 1999-14138	19981117
NO 2000002529	A		WO 1998-US24453	19981117
			NO 2000-2529	20000516
FI 2000001192	A		WO 1998-US24453	19981117
			FI 2000-1192	20000518
CZ 2000001822	A3		WO 1998-US24453	19981117
			CZ 2000-1822	19981117
EP 1062214	A1		EP 1998-958016	19981117
			WO 1998-US24453	19981117
SK 2000000738	A3		WO 1998-US24453	19981117
			SK 2000-738	19981117

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5955476	A	CIP of	US 5874448
AU 9914138	A	Based on	WO 9946258
CZ 2000001822	A3	Based on	WO 9946258
EP 1062214	A1	Based on	WO 9946258

PRIORITY APPLN. INFO: US 1998-42274 19980313; US 1997-976140 19971118
AN 1999-561651 [47] WPIDS
CR 1999-180042 [15]
AB WO 9946258 A UPAB: 20001209
NOVELTY - 2-(2,6-Dioxo-3-fluoropiperidin-3-yl)-isoindolines (I) are new.
DETAILED DESCRIPTION - Isoindolines of formula (I) and their acid addition salts are new.
Y = O or H2;
R1-R4 = H, halo, 1-4C alkyl, 1-4C alkoxy or amino.
ACTIVITY - Antiinflammatory; immunomodulator; antitumor; antimalarial; bronchodilator; cardiovascular; gastrointestinal; dermatological; antiarthritic; antiviral.
MECHANISM OF ACTION - Inflammatory cytokine inhibitor; tumor

necrosis factor alpha (TNF alpha) inhibitor; cyclic adenosine monophosphate (cAMP) modulator; nuclear factor kappa B inhibitor; phosphodiesterase inhibitor.

USE - For reducing undesirable levels of inflammatory cytokines (claimed), including TNF alpha , interleukin-1 (IL-1), IL-6 and **IL-12**.

(I) decrease levels of TNF alpha and increase cAMP levels, and are useful for treating or preventing a wide range of inflammatory, infectious, immunological or malignant diseases, including septic, endotoxic or hemodynamic shock, sepsis, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, conjunctivitis, atopic dermatitis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, human immunodeficiency virus (HIV) infection, other viral infections, acquired immunodeficiency syndrome (AIDS) and associated opportunistic infections, **rheumatoid arthritis**, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, radiation damage, hypoxic alveolar injury, asthma and myocardial infarction.

L18 ANSWER 7 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-508645 [42] WPIDS
CROSS REFERENCE: 1999-508653 [41]; 1999-518452 [41]; 1999-527366 [41]
DOC. NO. NON-CPI: N1999-379024
DOC. NO. CPI: C1999-148625
TITLE: Identifying nucleic acid that directly or indirectly modulates the immune response to a genetic vaccine vector, e.g. for prevention of infection or cancer.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): HOWARD, R; PUNNONEN, J; STEMMER, W P C; WHALEN, R G
PATENT ASSIGNEE(S): (MAXY-N) MAXYGEN INC
COUNTRY COUNT: 84
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9941368	A2	19990819	(199942)*	EN	104
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9926741	A	19990830	(200003)		
EP 1053312	A2	20001122	(200061)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9941368	A2	WO 1999-US3020	19990210
AU 9926741	A	AU 1999-26741	19990210
EP 1053312	A2	EP 1999-906948	19990210
		WO 1999-US3020	19990210

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9926741	A	Based on	WO 9941368
EP 1053312	A2	Based on	WO 9941368

PRIORITY APPLN. INFO: US 1998-74294 19980211; US 1998-21769 19980211

AN 1999-508645 [42] WPIDS

CR 1999-508653 [41]; 1999-518452 [41]; 1999-527366 [41]

AB WO 9941368 A UPAB: 20001128

NOVELTY - Identification of a polynucleotide (I) that modulates the immune response to a genetic vaccine vector (A), or encodes a polypeptide (II) with similar effect, comprises screening a library of recombinant polynucleotides to identify an optimized (I) having increased modulatory activity compared with non-recombinant polynucleotides from which the library was produced.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for identification of a polynucleotide (Ia) encoding an accessory molecule (IIa) that improves transport and presentation of antigen by a cell.

ACTIVITY - Antibacterial; antiviral; antifungal; anti-allergic; antidiabetic; anti-inflammatory; anti-arthritic; anti-asthma; anticancer; immunomodulatory.

MECHANISM OF ACTION - Induction of a specific immune response.

USE - Optimized (I) are incorporated into (A), or (I) or its encoded (II) are administered together with (A). (A) are used to treat or prevent infections (bacterial, viral or fungal); autoimmune disease (e.g. **rheumatoid arthritis**, diabetes or multiple sclerosis); other inflammatory conditions (e.g. psoriasis or pancreatitis); immune deficiency; allergy; asthma or cancer (including metastases). (I) are also used for recombinant production of (II).

ADVANTAGE - (I) make it possible to tailor an immune response to particular requirements, e.g. to direct a Th1-type helper response; to increase humoral or cellular responses (functioning as adjuvant); to control B or T cell proliferation; to induce immunogolobulin synthesis or isotype switching.

Searcher : Shears 308-4994

Dwg.0/15

L18 ANSWER 8 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-444317 [37] WPIDS
DOC. NO. CPI: C1999-130888
TITLE: Use of xanthine derivatives for treating e.g. chronic inflammatory diseases, chronic intestinal inflammation and arthritis.
DERWENT CLASS: B02
INVENTOR(S): KLAUS, S J; KLEIN, P J; KUMAR, A M
PATENT ASSIGNEE(S): (CELL-N) CELL THERAPEUTICS INC
COUNTRY COUNT: 31
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9936073	A1	19990722	(199937)*	EN	49
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN CZ HU IL JP MX NO NZ PL PT RU YU					
AU 9920987	A	19990802	(199954)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9936073	A1	WO 1998-US27848	19981230
AU 9920987	A	AU 1999-20987	19981230

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9920987	A	Based on	WO 9936073

PRIORITY APPLN. INFO: US 1998-8020 19980116
AN 1999-444317 [37] WPIDS
AB WO 9936073 A UPAB: 19990914
NOVELTY - Inhibiting **interleukin-12** signalling in mammal having CD4+Th1 cell-mediated inflammatory response comprises administration of a xanthine derivative (I).
DETAILED DESCRIPTION - Inhibiting **interleukin-12** signalling in a mammal having a CD4+ Th1 cell-mediated inflammatory response comprises administration of a xanthine derivative of formula (I) or its salt.
R1 = H, Me, sulphate, phosphate or salt thereof;
R2 = 1-12C alkyl, 1-11C alkoxyalkyl, dialkoxyalkyl, CH2C6H5, CH2-furan or biotin; and
R3 = H, CH3 or CH2C6H5.
ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.;

Antiarthritic; Antipsoriatic; Antiasthmatic; Immuno-suppressive; Antidiabetic; Neuroprotective; Antirheumatic; Dermatological; Antithyroid; Thyromimetic; Antiulcer. The effect of (R)-1-(5-hydroxyhexyl)-3,7-dimethyl xanthine (Ia) on decreasing the severity of paralysis in active models of murine experimental autoimmune encephalomyelitis (EAE) was evaluated. Active EAE was induced by immunization of female SJL/J mice with 800 mu g of mouse spinal cord homogenate. The mice were treated with (Ia) at 50 mg/kg or PBS by gavage twice daily for 15 days. In the control group, 7/10 animals developed hind limb paralysis with a mean clinical score of 2.4 on day 20. In the treated group, 2/13 animals developed paralysis with a mean clinical score of 0.75.

MECHANISM OF ACTION - Interleukin-**Antagonist**-12.

USE - (I) can be used for treating a chronic inflammatory disease, chronic intestinal inflammation, arthritis, psoriasis, asthma, autoimmune disorders (such as insulin-dependent diabetes mellitus, multiple sclerosis, **rheumatoid arthritis**, inflammatory bowel disease, lupus disorders and acute graft-versus-host disease), autoimmune thyroid diseases, such as Grave's disease and Hashimoto's disease, and inflammatory bowel diseases such as Crohn's disease and ulcerative colitis.

Dwg.0/12

L18 ANSWER 9 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-520957 [44] WPIDS
DOC. NO. CPI: C1998-156445
TITLE: Modulating responsiveness to corticosteroid e.g. in treating auto-immune diseases - by administering agent antagonising target that regulates production of interferon gamma.
DERWENT CLASS: B01 B04 B05
INVENTOR(S): BANERJEE, S; CARTER, A; GHAYUR, T; SEKUT, L; TRACEY, D E
PATENT ASSIGNEE(S): (BADI) BASF AG
COUNTRY COUNT: 81
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9841232	A2	19980924	(199844)*	EN	112
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9867604	A	19981012	(199907)		
NO 9904506	A	19991117	(200005)		
CZ 9903127	A3	20000315	(200021)		

Searcher : Shears 308-4994

EP 998300	A1	20000510 (200027)	EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE			
US 6054487	A	20000425 (200027)	
ES 2146192	T1	20000801 (200040)	
BR 9810409	A	20000822 (200050)	
CN 1269722	A	20001011 (200103)	
SK 9901221	A3	20001211 (200103)	
MX 9908433	A1	19991201 (200110)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9841232	A2	WO 1998-US4916	19980312
AU 9867604	A	AU 1998-67604	19980312
NO 9904506	A	WO 1998-US4916	19980312
		NO 1999-4506	19990917
CZ 9903127	A3	WO 1998-US4916	19980312
		CZ 1999-3127	19980312
EP 998300	A1	EP 1998-912929	19980312
		WO 1998-US4916	19980312
US 6054487	A	US 1997-820692	19970318
ES 2146192	T1	EP 1998-912929	19980312
BR 9810409	A	BR 1998-10409	19980312
		WO 1998-US4916	19980312
CN 1269722	A	CN 1998-805124	19980312
SK 9901221	A3	WO 1998-US4916	19980312
		SK 1999-1221	19980312
MX 9908433	A1	MX 1999-8433	19990914

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9867604	A	Based on	WO 9841232
CZ 9903127	A3	Based on	WO 9841232
EP 998300	A1	Based on	WO 9841232
ES 2146192	T1	Based on	EP 998300
BR 9810409	A	Based on	WO 9841232

PRIORITY APPLN. INFO: US 1998-16346 19980130; US 1997-820692 19970318

AN 1998-520957 [44] WPIDS

AB WO 9841232 A UPAB: 19981104

Modulating responsiveness to corticosteroids comprises administering: (a) an agent which antagonises a target that regulates production of interferon- gamma (IFN- gamma), to inhibit production of IFN- gamma and (b) a corticosteroid.

Preferably, the agent which antagonises a target that regulates

production of IFN- gamma is an IL-18 **antagonist** e.g. an inhibitor of a caspase family protease (especially an ICE inhibitor) or an antibody (fragment) or engineered binding protein that binds IL-18 or an IL-18 receptor. The agent may also be an **IL-12 antagonist** e.g. an agent that stimulates cyclic AMP production in cells that produce **IL-12**, especially a phosphodiesterase IV inhibitor such as a 4-arylpyrrolidinone, rolipram, denbufylline, tibenelast, nitraquazone, CP-80633, CP-77059 or a quinazolinedione or a beta -2 agonist such as salmeterol, fenoterol or isoproterenol.

USE- The process is used for treating septic shock, Crohn's disease, asthma, graft versus host disease or transplant rejection autoimmune disease or disorder and immunoinflammatory diseases or disorders comprising adult respiratory distress syndrome, systemic lupus erythematosus, inflammatory bowel disease, ulcerative colitis, multiple sclerosis, insulin dependent diabetes mellitus, **rheumatoid arthritis**, juvenile **rheumatoid arthritis**, psoriatic arthritis, inflammatory pulmonary syndrome, pemphigus vulgaris, idiopathic thrombocytopenic purpura, autoimmune meningitis, myasthenia gravis, autoimmune thyroiditis, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's syndrome, keratoconjunctivitis, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, Stevens-Johnson syndrome, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Graves ophthalmopathy,primary biliary cirrhosis, uveitis posterior and interstitial lung fibrosis. Administration is oral, intravenous or ophthalmic.

ADVANTAGE - The process reverses steroid resistance and increases steroid sensitivity.

Dwg.0/0

L18 ANSWER 10 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-312176 [27] WPIDS
DOC. NO. CPI: C1998-096289
TITLE: Treating or preventing diseases mediated by TNF-alpha - by co-administration of **antagonists** of TNF-alpha and **IL-12**, having synergistic effect in cases of e.g. **rheumatoid arthritis**, Crohn's disease and transplant disease.
DERWENT CLASS: B04 D16
INVENTOR(S): BRENNAN, F M; BUTLER, D M; FELDMANN, M; MAINI, R N; MALFAIT, A A M
PATENT ASSIGNEE(S): (KENN-N) KENNEDY INST RHEUMATOLOGY
COUNTRY COUNT: 80
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9822137	A1	19980528	(199827)*	EN	64
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9749599	A	19980610	(199843)		
EP 936923	A1	19990825	(199939)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9822137	A1	WO 1997-GB3151	19971117
AU 9749599	A	AU 1997-49599	19971117
EP 936923	A1	EP 1997-912367	19971117
		WO 1997-GB3151	19971117

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9749599	A	Based on	WO 9822137
EP 936923	A1	Based on	WO 9822137

PRIORITY APPLN. INFO: US 1996-749979 19961115

AN 1998-312176 [27] WPIDS

AB WO 9822137 A UPAB: 19980709

Method for treating or preventing a disease mediated by TNF alpha by co-administration of a TNF alpha **antagonist** (I) and an **IL-12 antagonist** (II).

USE - The method is used to treat (or prevent recurrence of) autoimmune, chronic or acute immune, inflammatory or neurodegenerative diseases, specifically **rheumatoid arthritis**, Crohn's disease and diseases associated with transplantation (of kidney, heart, marrow, liver, pancreas, small intestine, skin and lung,)infections, TNF-secreting cancers, cachexia and alcohol-induced, or other forms of, hepatitis (claimed).

ADVANTAGE - When used together, (I) and (II) provide a rapid and sustained alleviation of TNF-mediated disease, with significantly better response than when either component is used alone. This permits doses, and thus costs and side-effects, e.g. allergic responses, to be reduced.

Searcher : Shears 308-4994

Dwg.2A/7

L18 ANSWER 11 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998080866 EMBASE
TITLE: Cytokines in inflammatory bowel disease.
AUTHOR: Rogler G.; Andus T.
CORPORATE SOURCE: Dr. T. Andus, Department of Internal Medicine I, University of Regensburg, D-93042 Regensburg, Germany
SOURCE: World Journal of Surgery, (1998) 22/4 (382-389). Refs: 106
ISSN: 0364-2313 CODEN: WJSUDI
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English; French; Spanish
AB Cytokines play a central role in the modulation of the intestinal immune system. They are produced by lymphocytes (especially T cells of the Th1 and Th2 phenotypes), monocytes, intestinal macrophages, granulocytes, epithelial cells, endothelial cells, and fibroblasts. They have proinflammatory functions [interleukin-1 (IL-1), tumor necrosis factor (TNF), IL-6, IL-8, **IL- 12**] or antiinflammatory functions (interleukin-1 receptor **antagonist** (IL-1 **ra**), IL-4, IL-10, IL-11, transforming growth factor .beta. (TGF.beta.)]. Mucosal and systemic concentrations of many pro- and antiinflammatory cytokines are elevated in inflammatory bowel disease (IBD). An imbalance between proinflammatory and antiinflammatory cytokines was found for the IL-1/IL-1ra ratio in the inflamed mucosa of patients with Crohn's disease, ulcerative colitis, diverticulitis, and infectious colitis. Furthermore, the inhibition of proinflammatory cytokines and the supplementations with antiinflammatory cytokines reduced inflammation in animal models, such as the dextran sulfate colitis (DSS) model, the trinitrobenzene sulfonic acid (TNBS) model, or the genetically engineered model of IL-10 knockout mice. Based on these findings a rationale for cytokine treatment was defined. The first clinical trials using neutralizing monoclonal antibodies against TNF.alpha. (cA2) or the antiinflammatory cytokine IL-10 have shown promising results. However, many questions must be answered before cytokines can be considered standard therapy for IBD.

L18 ANSWER 12 OF 15 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-147515 [14] WPIDS
DOC. NO. NON-CPI: N1997-122015
DOC. NO. CPI: C1997-047130
TITLE: New **interleukin-12** beta-2

receptor and high binding affinity complexes - have a high affinity for **interleukin-12**, and are used to treat auto immune diseases.

DERWENT CLASS: B04 D16 S03
INVENTOR(S): GUBLER, U A; PRESKY, D H
PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE INC
COUNTRY COUNT: 20
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 759466	A2	19970226	(199714)*	EN	53
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 09132598	A	19970520	(199730)		43
EP 759466	A3	19970528	(199732)		
US 5840530	A	19981124	(199903)		
US 5852176	A	19981222	(199907)#		
US 5919903	A	19990706	(199933)		
JP 2948150	B2	19990913	(199943)		43

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 759466	A2		EP 1996-111807	19960723
JP 09132598	A		JP 1996-196385	19960725
EP 759466	A3		EP 1996-111807	19960723
US 5840530	A	Provisional	US 1995-1701	19950801
		Provisional	US 1996-18674	19960530
			US 1996-685118	19960723
US 5852176	A	Div ex	US 1996-685118	19960723
			US 1997-915495	19970820
US 5919903	A	Provisional	US 1995-1701	19950801
		Provisional	US 1996-18674	19960530
		Div ex	US 1996-685118	19960723
			US 1997-914520	19970819
JP 2948150	B2		JP 1996-196385	19960725

FILING DETAILS:

PATENT NO	KIND		PATENT NO
JP 2948150	B2	Previous Publ.	JP 09132598

PRIORITY APPLN. INFO: US 1996-18674 19960530; US 1995-1701 19950801; US 1996-685118 19960723; US 1997-915495 19970820; US 1997-914520 19970819

Searcher : Shears 308-4994

AN 1997-147515 [14] WPIDS
AB EP 759466 A UPAB: 19970407
A novel low binding affinity (BA) **interleukin-12** (**IL-12**) beta 2 receptor protein (A), or a fragment, has a low BA for **IL-12**, and when complexed with an **IL-12** beta 1 receptor protein (B), forms a complex having a high BA for **IL-12**. Also new are: (1) a complex with a high BA for **IL-12**, comprising (A) or a fragment, complexed with **IL-12** beta 1 receptor protein, or a fragment, which has a low BA for **IL-12**, and, when complexed with (A), has a high BA for **IL-12**; (2) a protein encoded by first and second nucleic acids, the first comprising two subsequences (SS), where one SS encodes a soluble fragment of (A), and the other SS (SS2) encodes all the domains of the constant region of the heavy chain of human Ig, except the first domain of the constant region, and the second nucleic acid has two SS, where one SS encodes a soluble fragment of (B) and the other SS is as for SS2; (3) nucleic acids encoding the proteins or complexes; (4) vectors contg. the nucleic acid of (3); (5) host cells transformed with the nucleic acid of (3); and (6) antibodies against (A) or (B).

USE - The proteins, complexes or antibodies may be used in therapeutic compsns., pref. with at least 1 cytokine **antagonists** (claimed). The compsns. are used to treat autoimmune dysfunctions (claimed), such as **rheumatoid arthritis**, inflammatory bowel disease and multiple sclerosis. The proteins or complexes can also be used to detect **antagonists** and agonists of **IL-12** activity (claimed).

Dwg.0/6

L18 ANSWER 13 OF 15 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:679814 SCISEARCH
THE GENUINE ARTICLE: VG269
TITLE: OPPOSITE EFFECTS OF INTERLEUKIN-13 AND INTERLEUKIN-12 ON THE RELEASE OF INFLAMMATORY CYTOKINES, CYTOKINE INHIBITORS AND PROSTAGLANDIN-E FROM SYNOVIAL FIBROBLASTS AND BLOOD MONONUCLEAR-CELLS
AUTHOR: SEITZ M (Reprint); LOETSCHER P; DEWALD B; TOWBIN H; BAGGIOLINI M
CORPORATE SOURCE: UNIV BERN, INSELSPITAL, DIV RHEUMATOL, CH-3010 BERN, SWITZERLAND (Reprint); UNIV BERN, THEODOR KOCHER INST, CH-3010 BERN, SWITZERLAND; CIBA GEIGY LTD, BASEL, SWITZERLAND
COUNTRY OF AUTHOR: SWITZERLAND
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (SEP 1996) Vol. 26, No. 9, pp. 2198-2202.
ISSN: 0014-2980.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 48
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We examined the effects of **interleukin-12** (**IL-12**) and interleukin-13 (IL-13) on cytokine, cytokine inhibitor and prostaglandin E (PGE) release from synovial fibroblasts and blood mononuclear cells (MNC). In resting synovial fibroblasts, we found that IL-13 is an inhibitor of IL-8 and PGE release. A significant decrease of PGE synthesis caused by IL-13 was also observed in tumor necrosis factor (TNF)-alpha-stimulated synovial fibroblasts, whereas **IL-12** had no regulatory effects on these cells. In resting and cytokine-stimulated MNC, IL-13 markedly inhibited TL-1 beta, IL-8 and monocyte chemoattractant protein-1 (MCP-1) release and potently stimulated interleukin-1 receptor **antagonist** (IL-1ra) synthesis. In contrast, **IL-12** stimulated the production of IL-1 beta and MCP-1 in TNF-alpha-stimulated. MNC and inhibited IL-1ra synthesis in cytokine-stimulated cells. These findings identify novel biological actions of **IL-12** and IL-13 on connective tissue and on blood mononuclear cells which indicate their regulatory functions as enhancer and suppressor of inflammatory processes, respectively.

L18 ANSWER 14 OF 15 MEDLINE
ACCESSION NUMBER: 94032770 MEDLINE
DOCUMENT NUMBER: 94032770
TITLE: Clinical and preclinical studies presented at the Keystone Symposium on Arthritis, Related Diseases, and Cytokines.
AUTHOR: Ralph P
CORPORATE SOURCE: Department of Immunology, Genentech, Inc., South San Francisco, CA 94080.
SOURCE: LYMPHOKINE AND CYTOKINE RESEARCH, (1993 Aug) 12 (4) 261-3.
Journal code: A3G. ISSN: 1056-5477.
PUB. COUNTRY: United States
Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402

AB Topics include treatment of multiple sclerosis (MS) with T cell receptor (TCR) peptides, **rheumatoid arthritis** (**RA**) with IL-1ra, IL-2 toxin conjugate, or antibodies to TNF, to CD4, or to ICAM-1, sepsis and five other diseases with IL-1ra, and treatment of experimental animal diseases with soluble receptors, **IL-12**, TGF-beta2, or small molecule **antagonists** of cytokines.

L18 ANSWER 15 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2

ACCESSION NUMBER: 93264853 EMBASE
DOCUMENT NUMBER: 1993264853
TITLE: Clinical and preclinical studies presented at the keystone symposium on arthritis, related diseases, and cytokines.
AUTHOR: Ralph P.
CORPORATE SOURCE: Department of Immunology, Genentech, Inc., 460 Point San Bruno Avenue,South San Francisco, CA 94080, United States
SOURCE: Lymphokine and Cytokine Research, (1993) 12/4 (261-263).
ISSN: 0277-6766 CODEN: LCREEY
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Topics include treatment of multiple sclerosis (MS) with T cell receptor (TCR) peptides, **rheumatoid arthritis** (**RA**) with IL-1ra, IL-2 toxin conjugate, or antibodies to TNF, to CD4, or to ICAM-1, sepsis and five other diseases with IL-1ra, and treatment of experimental animal diseases with soluble receptors, **IL-12**, TGF-.beta.2, or small molecule **antagonists** of cytokines.

(FILE 'MEDLINE' ENTERED AT 12:14:29 ON 06 MAR 2001)

L19 44171 SEA FILE=MEDLINE ABB=ON PLU=ON "ARTHRITIS, RHEUMATOID"/CT
L20 2762 SEA FILE=MEDLINE ABB=ON PLU=ON INTERLEUKIN-12/CT
L21 25 SEA FILE=MEDLINE ABB=ON PLU=ON L19 AND L20
L22 9 SEA FILE=MEDLINE ABB=ON PLU=ON L21 AND (DRUG THERAPY OR THERAPY OR THERAPEUTIC USE)/CT

L19 44171 SEA FILE=MEDLINE ABB=ON PLU=ON "ARTHRITIS, RHEUMATOID"/CT
L20 2762 SEA FILE=MEDLINE ABB=ON PLU=ON INTERLEUKIN-12/CT
L21 25 SEA FILE=MEDLINE ABB=ON PLU=ON L19 AND L20
L23 0 SEA FILE=MEDLINE ABB=ON PLU=ON L21 AND ADMINISTRATION & DOSAGE/CT

L22 ANSWER 1 OF 9 MEDLINE

Searcher : Shears 308-4994

AN 2000253024 MEDLINE
TI Intra-articular IL-10 gene transfer regulates the expression of collagen-induced arthritis (CIA) in the knee and ipsilateral paw.
AU Lubberts E; Joosten L A; Van Den Bersselaar L; Helsen M M; Bakker A C; Xing Z; Richards C D; Van Den Berg W B
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (2000 May) 120 (2) 375-83. Journal code: DD7. ISSN: 0009-9104.
AB We studied the effects of local IL-10 application, introduced by a recombinant human type 5 adenovirus vector, in the mouse knee joint during the early phase of CIA. One intra-articular injection with the IL-10-expressing virus (Ad5E1mIL-10) caused substantial over-expression of IL-10 in the mouse knee joint, using virus dosages which did not induce distracting inflammation. High expression of IL-10 was noted for a few days, being maximal at day 1. One intra-articular injection of Ad5E1mIL-10 in the knee joints of collagen type II (CII)-immunized mice, before onset of CIA was noted, reduced the incidence of collagen arthritis in that knee. Of high interest, the protective effect of local IL-10 expression by Ad5E1mIL-10 was not restricted to the knee joint alone. The arthritis incidence in the ipsilateral paw was highly suppressed. In contrast, local IL-10 over-expression was not effective when treatment was started after onset of CIA. Further analysis in the acute streptococcal cell wall-induced arthritis model revealed that local IL-10 over-expression markedly suppressed the production of tumour necrosis factor-alpha (TNF-alpha) and IL-1alpha, but had no significant effect on IL-1beta and IL-12 production in the inflamed synovium. These data indicate that local over-expression of IL-10 in the knee joint of mice regulates the expression of collagen arthritis, probably through down-regulation of TNF-alpha.

L22 ANSWER 2 OF 9 MEDLINE
AN 2000242900 MEDLINE
TI Bucillamine suppresses human Th1 cell development by a hydrogen peroxide-independent mechanism.
AU Morinobu A; Wang Z; Kumagai S
SO JOURNAL OF RHEUMATOLOGY, (2000 Apr) 27 (4) 851-8. Journal code: JWX. ISSN: 0315-162X.
AB OBJECTIVE: To clarify the effect of bucillamine, an antirheumatic drug related to D-penicillamine, on the development of human Th1 and Th2 cells in vitro. METHODS: Peripheral blood mononuclear cells (PBMC) or purified CD4+ T cells were subjected to the priming culture in which cells were stimulated with anti-CD3 and anti-CD28 monoclonal antibodies for 3 days and expanded for 4 days in the presence of interleukin-2. Cytokine production by the generated cells was determined on a flow cytometer using intracellular cytokine staining. The effects of bucillamine were determined by adding it for the first 3 days of the priming culture. RESULTS: Bucillamine decreased the frequency of interferon-gamma (IFN-gamma) producing CD4+ T cells among generated CD4+ T cells after the

priming culture of PBMC, although D-penicillamine did not. This effect of bucillamine was independent of hydrogen peroxide since it was not reversed by a catalase treatment. One of the bucillamine metabolites, SA981, which exerts its effects by a hydrogen peroxide-independent mechanism, decreased the frequency of IFN-gamma producing CD4+ T cells more potently than bucillamine. Bucillamine reduced the frequency of Th1 cells after the priming culture of purified CD4+CD45RO- T cells, indicating that bucillamine exerts the effect in the absence of monocytes or B cells. CONCLUSION: Bucillamine directly acts on CD4+CD45RO- T cells to suppress Th1 cell development by a hydrogen peroxide-independent mechanism. This previously unknown action may explain the in vivo effect of bucillamine in the treatment of rheumatoid arthritis.

L22 ANSWER 3 OF 9 MEDLINE
AN 2000155556 MEDLINE
TI Rheumatoid arthritis exacerbation caused by exogenous interleukin-12.
AU Peeva E; Fishman A D; Goddard G; Wadler S; Barland P
SO ARTHRITIS AND RHEUMATISM, (2000 Feb) 43 (2) 461-3. Journal code: 90M. ISSN: 0004-3591.
AB Interleukin-12 (IL-12) is a pleiotropic cytokine with proinflammatory, immunoregulatory, antitumor, and antimetastatic properties. It plays a crucial role in the development of the Th1 response and subsequent interferon-gamma production and enhancement of cell-mediated cytotoxicity. Recently, IL-12 has been used as an experimental therapy for cancer. Given the multiple immunomodulatory properties of IL-12, there are potential concerns associated with its clinical use. Of special interest are the possible side effects of IL-12 therapy in patients with autoimmune diseases, especially those that are T cell mediated, such as rheumatoid arthritis (RA). We present a case of severe RA exacerbation caused by treatment with IL-12 for metastatic cervical cancer. This is the first reported case of RA flare caused by exogenous IL-12.

L22 ANSWER 4 OF 9 MEDLINE
AN 2000074849 MEDLINE
TI The role of IL-12 in inflammatory activity of patients with rheumatoid arthritis (RA) [published erratum appears in Clin Exp Immunol 2000 Apr;120(1):224].
AU Kim W; Min S; Cho M; Youn J; Min J; Lee S; Park S; Cho C; Kim H; Kim WU/SS/[corrected to Kim W]; Min SY/SS/[corrected to Min S]; Cho ML/SS/[corrected to Cho M]; Min DJ/SS/[corrected to Min J]; Lee SH/SS/[corrected to Lee S]; Park SH/SS/[corrected to Park S]; Cho CS/SS/[corrected to Cho C]; Kim HY/SS/[corrected to Kim H]
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (2000 Jan) 119 (1) 175-81. Journal code: DD7. ISSN: 0009-9104.
AB The aim of this study was to investigate the role of IL-12 in patients with RA. IL-12 (p70) and its associated cytokines were

measured in sera and synovial fluid (SF) using an enzyme-linked immunosorbent method. Seven American College of Rheumatology (ACR) core set measures as well as IL-12 levels were sequentially monitored at the commencement and 4 months after treatment with a low-dose steroid and disease-modifying anti-rheumatic drugs (DMARDs). In sera, 64 (42.2%) of 152 RA patients had detectable concentrations of IL-12 (p70), whereas one (1.4%) of 69 osteoarthritis (OA) patients and five (10%) of 50 healthy controls had detectable IL-12 ($P < 0.001$). The median level of circulating IL-12 was also higher in RA patients ($P < 0.001$). In SF, the number of patients with detectable IL-12 and the median IL-12 levels were significantly higher in RA patients ($n = 53$) than in OA patients ($n = 22$). In paired samples ($n = 53$) of sera and SF from RA patients, IL-12 levels were higher in the SF than in sera ($P < 0.001$). Patients with detectable IL-12 ($n = 51$) in sera had higher tender joint scores ($P = 0.003$), swollen joint scores ($P < 0.001$) and C-reactive protein (CRP; $P = 0.036$), than those without ($n = 55$). Four months after treatment with DMARDs, the improved group showed a larger IL-12 decrease than the non-improved group ($P = 0.017$). The levels of IL-12 correlated positively with those of IL-2, interferon-gamma, IL-6, and tumour necrosis factor-alpha, but were correlated inversely with those of IL-10. Our results demonstrate that IL-12 levels reflect RA disease activity and that IL-12 is involved in the production of proinflammatory cytokines. An IL-12 blockade could be useful for the treatment of RA.

L22 ANSWER 5 OF 9 MEDLINE
AN 1999248217 MEDLINE
TI The beta2-adrenergic agonist salbutamol is a potent suppressor of established collagen-induced arthritis: mechanisms of action.
AU Malfait A M; Malik A S; Marinova-Mutafchieva L; Butler D M; Maini R N; Feldmann M
SO JOURNAL OF IMMUNOLOGY, (1999 May 15) 162 (10) 6278-83.
Journal code: IFB. ISSN: 0022-1767.
AB The therapeutic potential of salbutamol, a beta2-adrenergic agonist, was explored in collagen-induced arthritis. This study was based on a report that salbutamol, by elevating intracellular cAMP, inhibits IL-12 production by macrophages and dendritic cells, thus preventing Th1 development. Ten-week-old male DBA/1 mice were immunized by intradermal injection of type II collagen in CFA. Arthritis developed 15-30 days later and the mice were treated after onset of disease with salbutamol, 200 microgram i.p. After 10 days, the mice were sacrificed, and the hind paws were evaluated histologically. Salbutamol, 200 microgram daily or every other day, had a profound therapeutic effect on the clinical progression of arthritis, as assessed by clinical score and paw thickness. The therapeutic effect was dose dependent. Daily administration of 200 microgram of salbutamol offered the best protection against joint damage, as assessed by histology. In vitro, salbutamol reduced IL-12 and

TNF-alpha release by peritoneal macrophages in a dose-dependent manner, as well as TNF release by synovial cells from arthritic mice. Ex vivo, draining lymph node cells of the salbutamol-treated arthritic mice showed a diminished CII-specific IFN-gamma production and proliferation. In vivo, salbutamol specifically blocked mast cell degranulation in joint tissues. In conclusion, salbutamol has important effects on the immunoinflammatory response and a significant therapeutic action in collagen-induced arthritis.

L22 ANSWER 6 OF 9 MEDLINE
AN 1999137244 MEDLINE
TI Hypothalamic-pituitary-adrenocortical axis function in premenopausal women with rheumatoid arthritis not treated with glucocorticoids [see comments].
AU Cutolo M; Foppiani L; Prete C; Ballarino P; Sulli A; Villaggio B; Seriolo B; Giusti M; Accardo S
SO JOURNAL OF RHEUMATOLOGY, (1999 Feb) 26 (2) 282-8.
Journal code: JWX. ISSN: 0315-162X.
AB OBJECTIVE: To assess hypothalamic-pituitary-adrenocortical axis function in patients with rheumatoid arthritis (RA) not previously treated with glucocorticoids in relation to their inflammatory condition and in comparison to healthy controls. METHODS: We evaluated, in 10 premenopausal patients with RA and 7 age matched controls, plasma dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and cortisol concentrations, together with inflammatory cytokine levels [interleukin 6 (IL-6) and IL-12], both in basal conditions and after stimulation with ovine corticotropin releasing hormone (oCRH) and with low dose intravenous (5 microg) adrenocorticotropic hormone (ACTH). RESULTS: DHEA and DHEAS basal concentrations were found to be significantly lower ($p<0.05$) in premenopausal patients with RA than in controls. As expected, significantly higher basal levels of IL-6 and IL-12 ($p<0.05$) were found in patients with RA. After the low dose ACTH testing, the DHEA area under the curve value was found to be significantly lower ($p<0.01$) in patients than controls. Similar results, but without statistical significance, were observed after oCRH stimulation. DHEA levels at basal time showed a significant negative correlation with the erythrocyte sedimentation rate and platelet count, as well as with the Steinbrocker class of the disease ($p<0.05$). Normal plasma cortisol levels during oCRH and ACTH testing were found in patients with RA in spite of their inflammatory condition. After ACTH testing, IL-6 levels decreased significantly ($p<0.05$), whereas IL-12 levels were unchanged. No significant changes in IL-6 and IL-12 levels were found after oCRH testing. CONCLUSION: The abnormal androgen concentrations observed during testing in patients with RA might support the implication of adrenal androgens in the immune/inflammatory cytokine mediated mechanisms involved in the pathophysiology and clinical aspects of RA.

L22 ANSWER 7 OF 9 MEDLINE
AN 1999053095 MEDLINE
TI Combination therapy in mice: what can we learn that may be useful for understanding rheumatoid arthritis?.
AU Williams R O
SO SPRINGER SEMINARS IN IMMUNOPATHOLOGY, (1998) 20 (1-2) 165-80. Ref: 78
Journal code: VBG. ISSN: 0344-4325.

L22 ANSWER 8 OF 9 MEDLINE
AN 1998221008 MEDLINE
TI Pro- and anti-inflammatory cytokines in rheumatoid arthritis.
AU Isomaki P; Punnonen J
SO ANNALS OF MEDICINE, (1997 Dec) 29 (6) 499-507. Ref: 99
Journal code: AMD. ISSN: 0785-3890.
AB Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the accumulation of inflammatory cells into the synovium and the destruction of joints. Cytokines are important regulators of the synovial inflammation. Some cytokines, such as tumour necrosis factor (TNF)-alpha and interleukin (IL)-1, function by promoting inflammatory responses and by inducing cartilage degradation. Other cytokines, such as IL-4, IL-10 and IL-13, function mainly as anti-inflammatory molecules. Although anti-inflammatory cytokines are present in rheumatoid joints, in progressive RA their levels obviously are too low to neutralize the deleterious effects of proinflammatory cytokines. Inhibiting the action of proinflammatory cytokines by using specific cytokine inhibitors or anti-inflammatory cytokines is the basis for new therapies currently tested in patients with RA. Promising results on the use of neutralizing anti-TNF-alpha monoclonal antibodies in the treatment of RA have been reported. The results from a trial using recombinant IL-10 in the treatment of patients with RA are available in the near future and will be important in determining the therapeutic potential of this cytokine.

L22 ANSWER 9 OF 9 MEDLINE
AN 97130989 MEDLINE
TI An open study of pentoxyfylline and thalidomide as adjuvant therapy in the treatment of rheumatoid arthritis.
AU Huizinga T W; Dijkmans B A; van der Velde E A; van de Pouw Kraan T C; Verweij C L; Breedveld F C
SO ANNALS OF THE RHEUMATIC DISEASES, (1996 Nov) 55 (11) 833-6.
Journal code: 62W. ISSN: 0003-4967.
AB OBJECTIVE: Dysregulation of tumour necrosis factor alpha (TNF alpha) production is thought to be important in rheumatoid arthritis. Since pentoxifylline and thalidomide inhibit endotoxin induced TNF production in vitro, these drugs were tested in an open study in rheumatoid arthritis patients to assess toxicity, the effect on TNF production, and the antiarthritic effects. METHODS: 12 patients with

active rheumatoid arthritis were treated with 1200 mg pentoxifylline and 100 mg thalidomide a day during 12 weeks. In addition, TNF production was assessed by ex vivo whole blood cultures stimulated with endotoxin. RESULTS: Adverse events such as xerostomia, drowsiness, and constipation occurred in almost all patients, which led to discontinuation in three. The drugs halved the TNF production capacity during treatment (ANOVA, P < 0.03) whereas production capacity of interleukin (IL) 6, IL-10, and IL-12 was not affected. Of the nine patients who completed the study, five fulfilled the ACR-20% response criteria after 12 weeks of treatment. CONCLUSIONS: Although pentoxifylline/thalidomide reduced the production capacity of TNF, the benefit/side effects ratio was poor due to multiple adverse effects, while clinical observation suggests limited efficacy.

(FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:16:23 ON 06 MAR 2001)

```
L24         5971 S LEONARD J?/AU
L25         4477 S GOLDMAN S?/AU
L26          615 S (OHARA R? OR O HARA R?)/AU
L27            2 S L24 AND L25 AND L26
L28           65 S L24 AND (L25 OR L26)
L29            2 S L25 AND L26
L30        10996 S L24 OR L25 OR L26
L31            1 S (L28 OR L30) AND L5
L32            2 S L27 OR L29 OR L31
L33            1 DUP REM L32 (1 DUPLICATE REMOVED)
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- Author (s)

L33 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

ACCESSION NUMBER: 1995:934127 CAPLUS
DOCUMENT NUMBER: 123:337469
TITLE: Use of **IL-12** and **IL-12** antagonists in treatment of autoimmune diseases
INVENTOR(S): **Leonard, John P.; Goldman, Samuel; O'Hara, Richard, Jr.**
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
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AB Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, **rheumatoid arthritis**, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering **IL-12** or an **IL-12** antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with **IL-12** during restimulation, and alleviated by injection of a polyclonal antibody to **IL-12**.

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